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A Thesis Entitled

Tetrafluoropyridazine: A Scaffold for the Synthesis of Highly Functionalised Heterocycles

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A Candidate for the Degree of Doctor of Philosophy 2008

Declaration

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Part of this work has been the subject of the following:

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I'd like to use this opportunity to thank everyone who have made the last three years so fantastic. I'm sure I'll forget someone but everyone in the department has had a part to play in making it such a stimulating place to work.

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Finally, and most importantly, I must thank my Mam and my brother Ian for all their support, enthusiasm and interest throughout my whole time at university.

Abbreviations

Å	Ångstrom
Ac	Acetyl
Ar	Aryl
Asn	Asparagine
BINAP	2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
Bn	Benzyl
BOC	<i>t</i> -Butyloxycarbonyl
Bu	Butyl
cat	Catalyst
Cbz	Carboxybenzyl
COD	Cyclooctadiene
conc	Concentrated
Cy	Cyclohexyl
d	Days
dba	Dibenzylidene Acetone
DCE	1,2-Dichloroethane
DCM	Dichloromethane
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DHQD	Dihydroquinidine
DIPEA	<i>Diisopropylethylamine</i>
DMA	Dimethylacetamide
DMAP	<i>N,N</i> -dimethyl-4-aminopyridine
DME	Dimethoxyethane
DMF	Dimethylformamide
DMG	Directed Metallation Group
DMSO	Dimethyl sulfoxide
DoM	Directed <i>ortho</i> Metallation
dppe	1,2-Bis(diphenylphosphino)ethane
E	Electrophile
ED ₅₀	Effective Dose

EI	Electron Ionisation
eq	Equivalents
ES	Electrospray
Et	Ethyl
FMO	Frontier Molecular Orbital
Fmoc	Fluorenylmethyloxycarbonyl
GC-MS	Gas Chromatography – Mass Spectrometry
h	Hours
HMDS	Hexamethyldisilazane
HOMO	Highest Occupied Molecular Orbital
HPLC	High Performance Liquid Chromatography
Ile	Isoleucine
IR	Infrared
J	Coupling Constant / Hz
k_{rel}	Relative Rate Constant
L	Ligand
LCD	Liquid Crystal Display
LC-MS	Liquid Chromatography – Mass Spectrometry
LDA	Lithium Diisopropylamide
Leu	Leucine
log P	Lipophilicity
LTMP	Lithium 2,2,6,6-Tetramethylpiperidide
LUMO	Lowest Unoccupied Molecular Orbital
MDAP	Mass Directed Automated Purification
Me	Methyl
MeCN	Acetonitrile
min	Minutes
mol	Moles
mp	Melting Point
MW	Microwave
NMO	<i>N</i> -Methylmorpholine <i>N</i> -Oxide
NMP	<i>N</i> -Methylpyrrolidone
NMR	Nuclear Magnetic Resonance Spectroscopy

Nuc	Nucleophile
<i>o</i> -DCB	1,2-Dichlorobenzene
OLED	Organic Light Emitting Diode
OTf	Triflate
Ph	Phenyl
pin	Pinacol ester
pK _a	Acid Dissociation Constant
ppm	Parts Per Million
Pr	Propyl
R	Alkyl
rt	Room Temperature
S _N Ar/ S _N AE	Nucleophilic Aromatic Substitution
t _½	Half-life
TBS	Tributylsilyl
THF	Tetrahydrofuran
THP	Tetrahydropyran
TFA	Trifluoroacetic Acid
TLC	Thin Layer Chromatography
TMS	Trimethylsilyl
Trp	Tryptophan
Ts	Tosyl
UV	Ultraviolet
X	Halogen
XANTPHOS	4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene
Δ	Heat
δ	Chemical Shift / ppm
))))	Ultrasound

Contents

Declaration	i
Acknowledgements	ii
Abbreviations	iii
Contents	vi
Abstract	x
Chapter 1: The Synthesis and Chemistry of Pyridazine Derivatives	1
1.1 Aromatic Heterocycles	1
1.1.1 Reactivity of Aromatic Heterocycles	1
1.1.2 The Diazines	4
1.1.3 Oxy-heteroaromatics	5
1.2 Uses of Pyridazine Derivatives	6
1.2.1 Pyridazine Derivatives in Medicinal Chemistry	6
1.2.2 Pyridazine Derivatives in Materials Chemistry	8
1.2.3 Pyridazine Derivatives as Ligands	8
1.3 Syntheses of Pyridazine Derivatives	9
1.3.1 Condensation of 1,4-Dicarbonyl Compounds with Hydrazine	10
1.3.2 Cycloadditions of 1,2,4,5-Tetrazines	14
1.4 Functionalisation of Pyridazine Rings	21
1.4.1 Palladium Catalysed Cross-Coupling Processes	21
1.4.2 Metallation	28
1.4.3 Nucleophilic Aromatic Substitution	33
1.5 Ring Fused Pyridazine Systems	36
1.5.1 Cyclisation Step forms Pyridazine Ring	36
1.5.2 Cyclisations of Suitable 1,2-Difunctional Pyridazines	38
1.5.3 Cyclisations Involving Pyridazine Ring Nitrogen	41
1.5.4 Cyclisations Onto Unfunctionalised Pyridazine Rings	42
1.6 Fluorinated Pyridazine Derivatives	43
1.7 Fluorine in Medicinal Chemistry	46

	<i>Contents</i>
1.7.1 Effects of Fluorine on Physicochemical Properties	47
1.7.2 Effects of Fluorine on Metabolism	49
1.7.3 Effects of Fluorine on Protein Binding	50
1.8 Conclusion	53
Chapter 2: Syntheses of Polyfunctional Pyridazin-3(2<i>H</i>)-one Systems from Tetrafluoropyridazine	54
2.1 Aims and Approach	54
2.2 Polysubstituted Pyridazin-3(2 <i>H</i>)-one Derivatives	56
2.3 Synthesis and Structure of 4,5,6-Trifluoropyridazin-3(2 <i>H</i>)-one	58
2.4 Nucleophilic Substitution Reactions of 4,5,6-trifluoropyridazinone	60
2.4.1 Nucleophilic Substitution Reactions with Amines	61
2.4.2 Nucleophilic Substitution Reactions with Thiolate Ions	68
2.4.3 Nucleophilic Substitution Reactions with Basic Nucleophiles	69
2.5 Syntheses of Disubstituted Pyridazin-3(2 <i>H</i>)-one Derivatives	70
2.5.1 Reactions of 4-Morpholino-5,6-difluoropyridazin-3(2 <i>H</i>)-one with Amine Nucleophiles	70
2.5.2 Reaction of 4-(4-bromophenylamino)-5,6-difluoropyridazin-3(2 <i>H</i>)-one with Amine Nucleophiles	72
2.5.3 Reaction of 4-butylamino-5,6-difluoropyridazin-3(2 <i>H</i>)-one and 4-benzylamino-5,6-difluoropyridazin-3(2 <i>H</i>)-one with Amine Nucleophiles	74
2.5.4 Substitutions on 5-substituted-4,6-difluoropyridazin-3(2 <i>H</i>)-ones	79
2.5.5 Reaction of Monosubstituted Pyridazin-3(2 <i>H</i>)-ones with oxygen nucleophiles	81
2.6 Displacement of Fluorine from 6-Fluoro-4,5-diamino Pyridazin-3(2 <i>H</i>)-one Systems	83
2.7 Conclusion	84
Chapter 3: Chemistry of <i>N</i>-Functionalised Polyfluoropyridazin-3(2<i>H</i>)-one Derivatives	86
3.1 Introduction	86

3.2 Attempted Alkylation of 4,5,6-Trifluoropyridazin-3(2 <i>H</i>)-one	87
3.3 <i>N</i> -Arylation of 4,5,6-trifluoropyridazin-3(2 <i>H</i>)-one	88
3.4 <i>N</i> -Protected Pyridazin-3(2 <i>H</i>)-ones	93
3.5 Conclusion	99
Chapter 4: Syntheses of Ring-Fused Pyridazine Systems from Tetrafluoropyridazine	101
4.1 Introduction	101
4.2 Reactions of Tetrafluoropyridazine with 1,2-Dinucleophiles	102
4.2.1 Nitrogen Containing 1,2-Dinucleophiles	102
4.2.2 Sulfur Containing 1,2-Dinucleophiles	104
4.2.3 Oxygen Containing 1,2-Dinucleophiles	104
4.2.4 Reactions of 4,5,6-Trifluoropyridazin-3(2 <i>H</i>)-one with dinucleophiles	108
4.3 Reactions of [6,6]-Ring Fused Scaffolds with Nucleophiles	110
4.4 Reactions of Tetrafluoropyridazine with 1,1-Dinucleophiles	113
4.4.1 Reactions of Tetrafluoropyridazine with Amidine and Thioamide Derivatives	114
4.4.2 Reaction of Tetrafluoropyridazine with 2-Aminopyridine Derivatives	117
4.5 Functionalisation of [5,6]-Ring Fused Scaffolds	119
4.5.1 Functionalisation of 1 <i>H</i> -Imidazo[4,5- <i>d</i>]pyridazine Systems	120
4.5.2 Functionalisation of Tetraazafluorene Scaffolds	124
4.6 Conclusion	128
Chapter 5: Chemistry of Tetrachloropyridazine	130
5.1 Introduction	130
5.2 Synthesis of Tetrachloropyridazine	131
5.3 Nucleophilic Aromatic Substitution Reactions of Tetrachloropyridazine	131
5.3.1 Monosubstitution	131
5.3.2 Disubstitution	136
5.4 Ring Fused Systems from Tetrachloropyridazine	137
5.5 Metallation	139

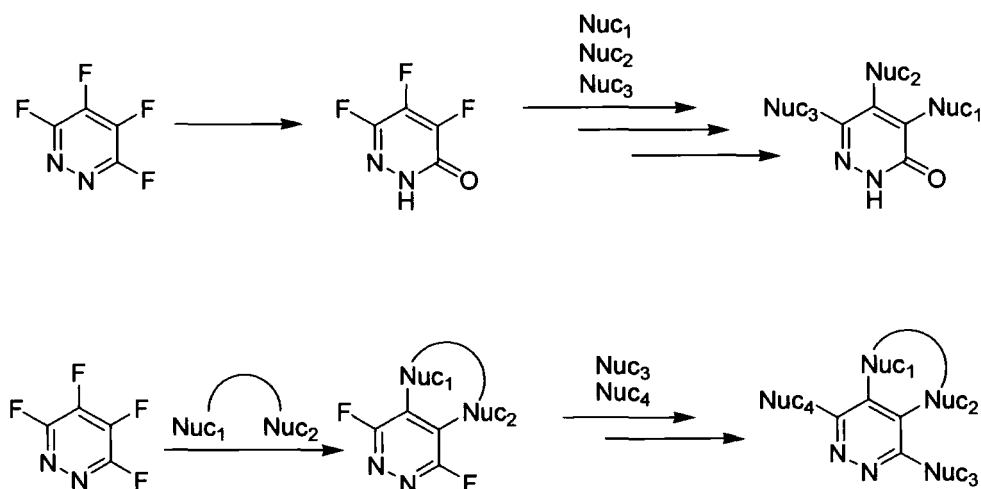
	<i>Contents</i>
5.6 Palladium Catalysed Cross-Coupling Reactions	140
5.7 Conclusion	144
Chapter 6: Conclusion	146
Chapter 7: Experimental	150
7.1 Technical Details	150
7.2 Experimental to Chapter 2	154
7.3 Experimental to Chapter 3	184
7.4 Experimental to Chapter 4	198
7.5 Experimental to Chapter 5	222
References	235
 Attached CD-ROM	
 Appendix 1: X-ray Crystal Structure Data	
Appendix 2: Calculated Lipinski Parameters for Molecules Synthesised	

Abstract

There is a great desire for the synthesis of new heteroaromatic compounds, which have a range of applications from pharmaceuticals to materials. These industries require large numbers of heterocyclic derivatives for their screening programmes, however many common routes for the synthesis of aromatic heterocycles do not allow for the flexible introduction of a diverse range of substituents.

Our approach involves the use of tetrafluoropyridazine as a scaffold for the synthesis of a diverse range of heteroaromatic systems. Perfluorinated heteroaromatic compounds, such as tetrafluoropyridazine, are highly reactive towards displacements by nucleophilic species. Sequential nucleophilic aromatic substitution reactions of 4,5,6-trifluoropyridazin-3(2*H*)-one have been studied and a range of polysubstituted systems synthesised. Similarly, reactions of tetrafluoropyridazine with dinucleophiles have been utilised to yield ring-fused products, many of which are rare heterocyclic substructures.

This approach has allowed the synthesis of a small library of compounds based on the pyridazine ring system with moderate skeletal and substituent diversity. The synthesis of some non-halogenated products by displacement of all ring fluorine atoms has also been reported.



Chapter 1

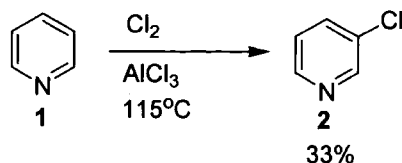
The Synthesis and Chemistry of Pyridazine Derivatives

1.1 Aromatic Heterocycles

The use of aromatic heterocycles has become ubiquitous in recent years in a variety of applications, ranging from pharmaceuticals to materials and, as a result, the chemistry of heteroaromatic systems has been studied in detail. This thesis discusses the chemistry of highly fluorinated pyridazines, one class of heterocycle that has undergone little study in the past. Consequently, this chapter will offer a general introduction to heteroaromatic chemistry, before a more detailed discussion of pyridazine chemistry and corresponding fluorinated systems.

1.1.1 Reactivity of Aromatic Heterocycles

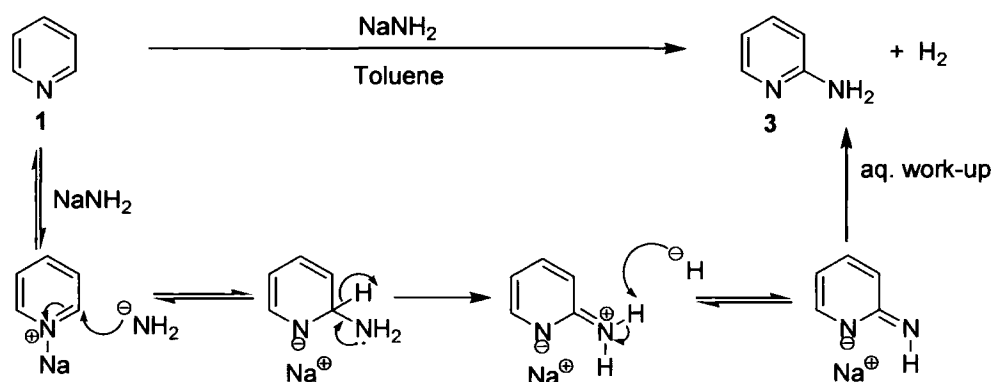
The chemistry of benzene and five membered heteroaromatic rings such as pyrrole¹ are dominated by electrophilic aromatic substitution, due to the electron rich nature of the aromatic ring. However, in the case of six membered nitrogen heteroaromatics, which are the focus of this thesis, electrophilic aromatic substitution reactions proceed extremely slowly and, in many cases, not at all. Instead these heterocycles, such as pyridine, react with electrophiles, such as methyl iodide, at the ring nitrogen, forming, for example, positively charged pyridinium salts². Under relatively forcing conditions, electrophilic substitution at a carbon atom of the pyridine ring can proceed, for example 3-chloropyridine **2** is produced by reaction of pyridine **1** with chlorine gas and aluminium (III) chloride at 115°C³ (Scheme 1.1), but these reactions are extremely difficult to perform as the pyridinium cations produced initially are highly unreactive towards electrophiles.



Scheme 1.1

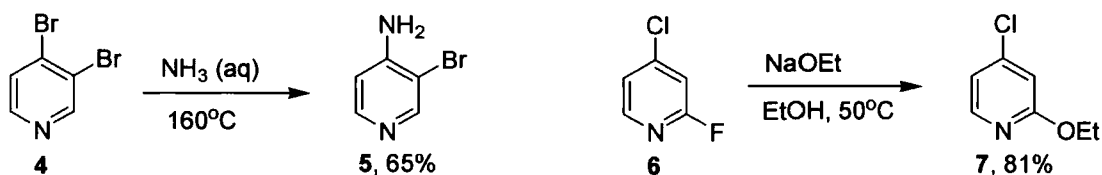


Instead, the chemistry of six membered nitrogen heteroaromatics is dominated by reactions involving nucleophilic species. For example, pyridine derivatives react with sodium amide at the 2-position to yield 2-amino pyridine systems **3**. This is known as the Chichibabin reaction⁴, and formally involves the nucleophilic substitution of hydride ion by the powerful anionic nucleophile NH_2^- (Scheme 1.2).



Scheme 1.2

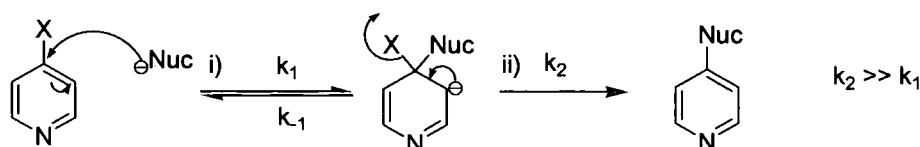
Nucleophilic substitution reactions involving pyridine and related heterocyclic derivatives proceed much more efficiently when a good leaving group is attached to the site of nucleophilic attack. This is typically halide, although sulfonyl, nitro and alkoxy groups may also be used⁵. The highest reactivity towards nucleophilic displacement is observed when the leaving group is present at a position α - or γ - to the ring nitrogen. For example, 3,4-dibromopyridine **4** reacts selectively with ammonia at the 4-position. Also, fluorine is more readily displaced than heavier halogens, demonstrated by selective displacement of the fluorine atom of 2-fluoro-4-chloropyridine **6** with alkoxide nucleophiles (Scheme 1.3)⁶.



Scheme 1.3

These observations can be explained by consideration of the mechanism of nucleophilic aromatic substitution of halogenated pyridine systems. The presence of the

electronegative ring nitrogen means that pyridine carbon atoms are much more electron deficient than in benzene systems, and are therefore susceptible to attack by nucleophiles. Well established nucleophilic aromatic substitution reactions proceed *via* an addition-elimination mechanism (S_NAr or S_NAE) comprising of two key steps (Scheme 1.4); i) slow, reversible attack of the nucleophile to form a negatively charged, tetrahedral intermediate known as a Meisenheimer complex, and ii) elimination of the leaving group to form the substituted product.



Scheme 1.4

Although generally short lived intermediates, Meisenheimer complexes have been isolated and characterised spectroscopically, particularly in the case of activated polynitrobenzenes **8** (Figure 1.1)^{7,8}.

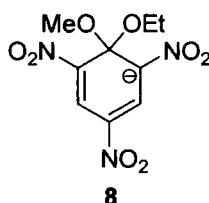
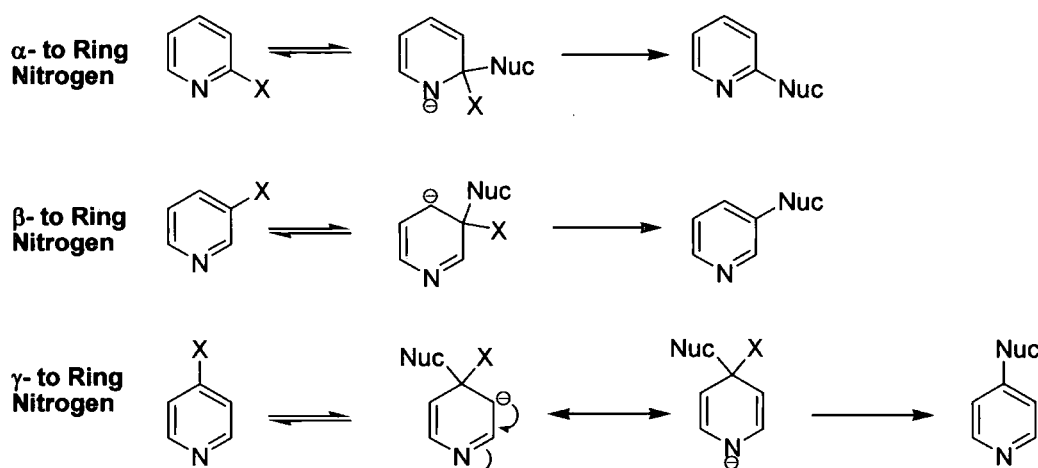


Figure 1.1

The observation that the displacement of halide in halogenated systems proceeds in the order $F \gg Cl \sim Br > I$ provides further evidence for the above mechanism⁹. It is well established that the bond strength of C-X bonds decreases in the order $C-F > C-Cl > C-Br > C-I$ and, therefore, the high reactivity of fluorine towards nucleophilic displacement suggests that bond breaking does not occur in the rate determining step. Consequently, addition of the nucleophile must be rate determining. This step is accelerated in more electron deficient heterocycles, which is supported by the fact that fluorine is the most electronegative of the halogens.

The preference for substitution α - and γ - to ring nitrogen in halogenated heteroaromatic derivatives can be explained by the stability of the corresponding Meisenheimer intermediates² (Scheme 1.5). The negative charge can be stabilised *via* delocalisation onto the electronegative ring nitrogen for α - and γ -substituted systems, but this is not possible when the halogen atom is β - to ring nitrogen. Substitution, therefore, proceeds *via* the most stable Meisenheimer intermediate.



Scheme 1.5

1.1.2 The Diazines

This thesis is concerned with the production of highly functionalised pyridazine systems from tetrafluoropyridazine, so a brief discussion of diazine chemistry is appropriate before pyridazines are considered in more detail. The structures of the three diazines (pyridazine, pyrimidine and pyrazine) consist of two nitrogen atoms in a six membered aromatic ring (Figure 1.2).

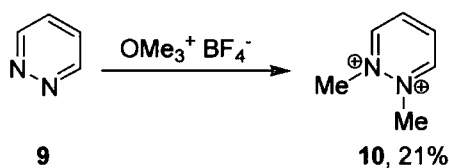


Figure 1.2

The basicity of the diazines is reduced, relative to pyridine, due to the electron withdrawing effect of the second ring nitrogen destabilising the protonated cation. Of the three diazines, pyridazine is the most basic, this is hypothesised to be due to the 'alpha effect' whereby reduced repulsion of the two adjacent nitrogen lone pairs slightly stabilises the protonated form¹⁰.

Diazines are correspondingly more reactive towards nucleophilic substitution than pyridine systems, due to the additional electron withdrawing effect of the second ring nitrogen². Again, sites α - and γ - to ring nitrogen are activated towards nucleophilic attack, in other words, all sites in diazines are activated except for the 5-position of pyrimidines. Therefore, halogen substituents at both the 3- and 4-positions in pyridazine derivatives are expected to be highly reactive towards nucleophilic displacement.

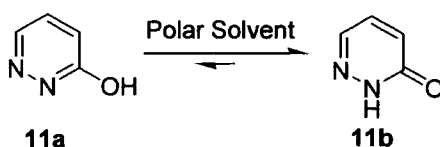
The diazines are less reactive towards electrophiles than pyridine derivatives, which is reflected in their lower basicity. In general, electrophilic attack occurs *via* addition to ring nitrogen to give diazinium cations. Addition to both ring nitrogens is generally extremely difficult as this would result in the formation of a dication **10**, although it is possible with powerful alkylating agents such as trialkyloxonium salts (Scheme 1.6)¹¹. Electrophilic substitution at carbon in diazines is rare, although some halogenation reactions are known, requiring extremely forcing conditions.



Scheme 1.6

1.1.3 Oxy-heteroaromatics

Oxy-pyridines and oxy-diazines generally exist as the keto tautomer, and are known as pyridones or diazinones. The pyridone tautomer is favoured by the use of polar solvents such as acetonitrile and water, whilst in hydrocarbon solvents and the gas phase the hydroxy-pyridine tautomer is favoured (Scheme 1.7)¹².



Scheme 1.7

The degree of aromaticity of oxy-heteroaromatic systems depends on the relative contribution of the pyridazinium canonical form. Calculations on 2-pyridone suggest that it is only around 25 kJ mol^{-1} less aromatic than pyridine itself¹³ and similar X-ray crystal structure analysis has estimated that pyridazin-3(2*H*)-one **11b** to be around 20 kJ mol^{-1} less aromatic than 3-hydroxypyridazine **11a**¹⁴. These results suggest that solvation factors are significant in favouring the slightly less aromatic pyridazinone tautomer.

1.2 Uses of Pyridazine Derivatives

Pyridazine based systems have been shown to have numerous practical applications, and the forthcoming section will outline some of these.

1.2.1 Pyridazine Derivatives in Medicinal Chemistry

Heteroaromatic scaffolds, such as pyridazine derivatives, have been shown to be 'privileged structures' in medicinal chemistry, and many drug discovery programmes utilise a pyridazine as a core scaffold. Examples are far too numerous to give more than a flavour of the chemistry reported in the literature in this section, however it should be noted that pyridazine based systems are less common in the literature than those based on pyridine or the other diazines.

Examples of commercially available pharmaceutical pyridazines (Figure 1.3) include hydralazine¹⁵, an antihypertensive which acts as a vasodilator, azelastine¹⁵, a bronchodilator used in the treatment of asthma, and minaprine¹⁶, an antidepressant which acts as an acetylcholinesterase inhibitor.

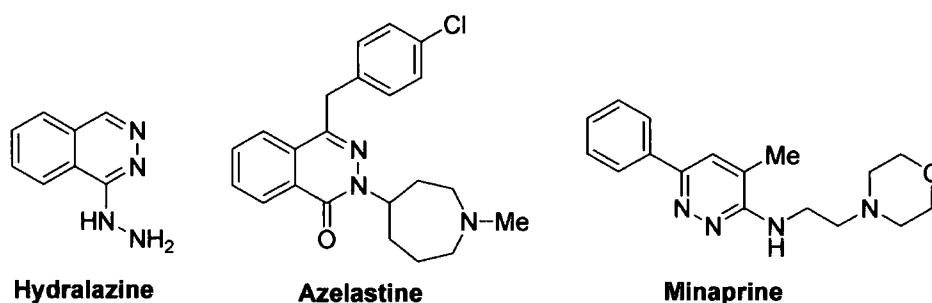


Figure 1.3

Various pyridazine based heterocyclic scaffolds have been utilised in recent medicinal chemistry programmes against a range of biological targets and physiological effects (Figure 1.4). The phthalazinone **12** has been screened as an anti-HIV agent¹⁷, whilst the activity of **13** for the treatment of cancer by inhibiting the repair of DNA in cancer cells damaged by radiotherapy has been examined^{18, 19}. **14** has been shown to act as a selective agonist at the GABA_A receptor α_3 subunit, with potential application in the treatment of anxiety²⁰. Compound **15** entered Phase 2 clinical trials as a diuretic antihypertensive agent²¹, whilst **16** shows antifungal activity against a range of species²². **17** has been demonstrated to be a potential agent for pain relief²³.

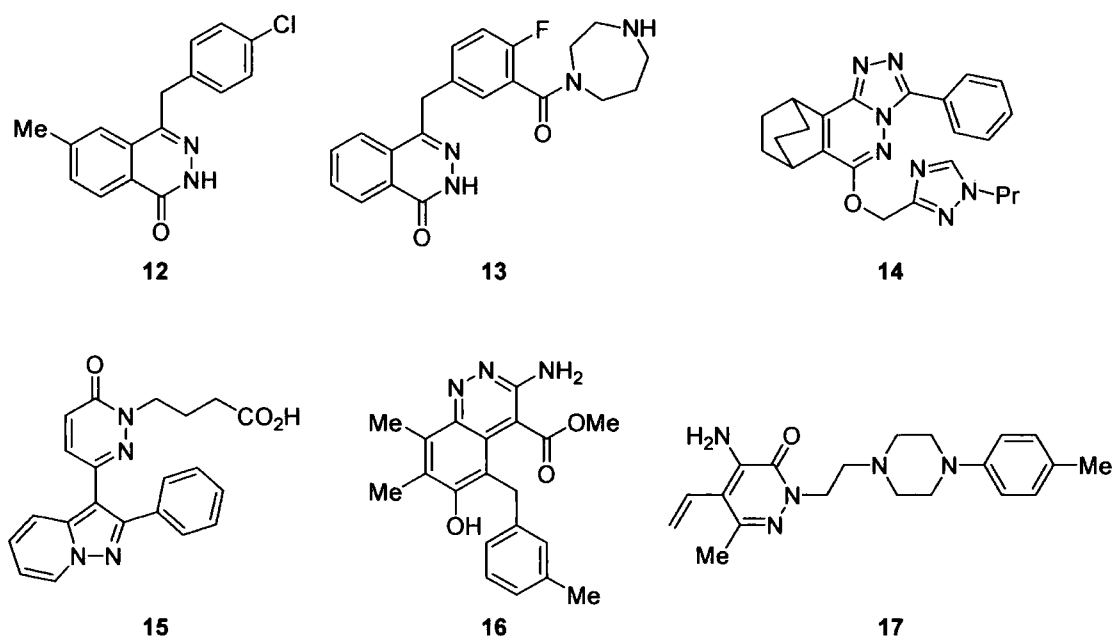


Figure 1.4

1.2.2 Pyridazine Derivatives in Materials Chemistry

Various aromatic heterocycles, including pyridazine systems, have been utilised in materials chemistry, in applications including liquid crystal displays (LCDs) and as organic light emitting diode devices (OLEDs).

There is a particular need for molecules which emit blue light in electroluminescent displays. A family of pyrrolopyridazine derivatives have been synthesised as potential small molecule blue emitters²⁴. Compound **18** (Figure 1.5) was shown to emit light in the blue wavelengths of the spectrum, and had the best quantum yield of the compounds screened in the library.

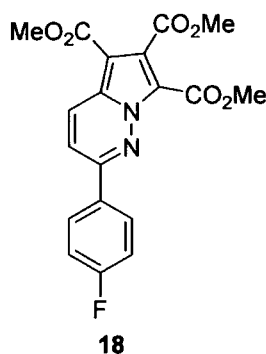


Figure 1.5

1.2.3 Pyridazine Derivatives as Ligands

Pyridazine derivatives have been utilised as ligands for binding to metal atoms, with application in catalysis, medicinal chemistry and supramolecular chemistry. For example phthalazine ligand **19** has been developed as a ligand for osmium in the Sharpless asymmetric dihydroxylation reaction of alkenes, giving the diol with excellent enantioselectivity²⁵. Lanthanum-(III) complexes of phthalazin-1(2*H*)-one **20**, which bind *via* carbonyl oxygen, have been shown to have DNA binding ability which leads to antitumour activity²⁶ (Figure 1.6).

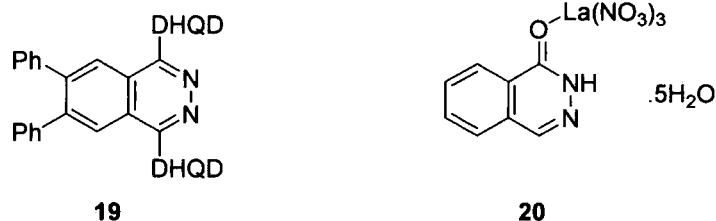


Figure 1.6

Ligand **21** has been developed with the ability to bind up to four copper ions to form multimetallic complexes²⁷. Meanwhile, coordination polymers have been synthesised from pyridazino[4,5-*d*]-pyridazine **22**²⁸ and 4,4'-bipyridazine **23**²⁹ in reaction with Cu²⁺, Zn²⁺ and Ag⁺ ions to give bridged and ladder supramolecular assemblies (Figure 1.7).

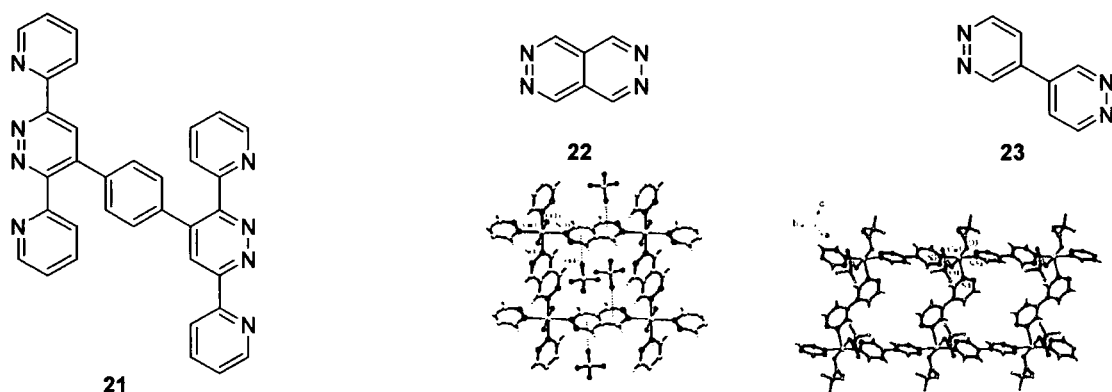
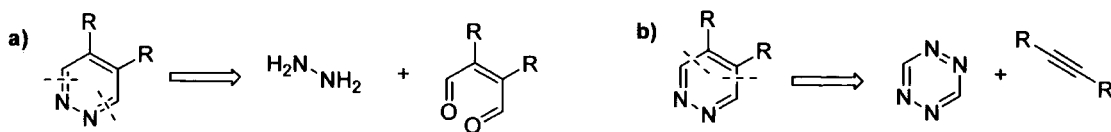


Figure 1.7

1.3 Syntheses of Pyridazine Derivatives

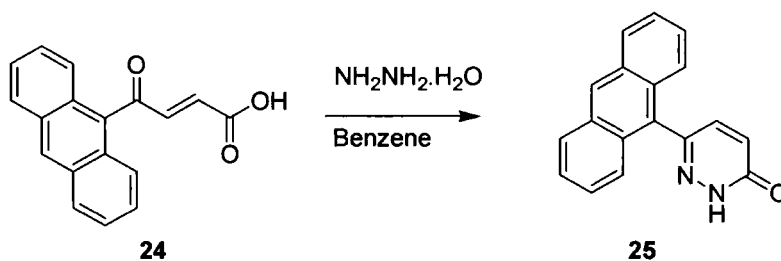
The pyridazine ring system can be assembled by two main routes (Scheme 1.8). The obvious disconnection is at the two imine type nitrogens, yielding a 1,4-dicarbonyl compound and hydrazine (Route a), whilst another common approach is *via* the cycloaddition of 1,2,4,5-tetrazines with dienophiles (Route b), proceeding with loss of molecular nitrogen. The forthcoming section will describe both of these approaches in detail.



Scheme 1.8

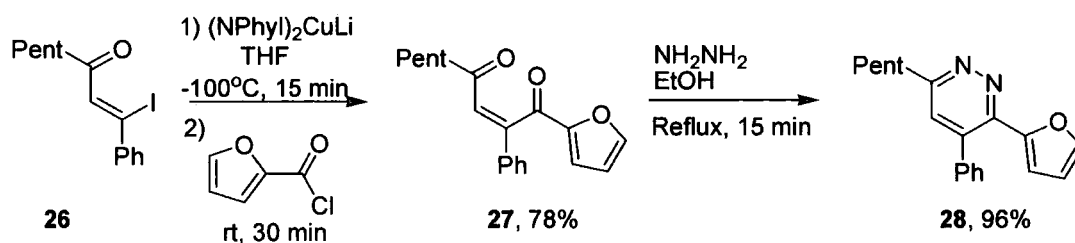
1.3.1 Condensation of 1,4-Dicarbonyl Compounds with Hydrazine

For a 1,4-dicarbonyl compound to yield a pyridazine directly, there must be a double bond at the position β - to both carbonyl groups. Although these unsaturated dicarbonyl derivatives are less common than their saturated counterparts, they have been widely utilised in the synthesis of pyridazine systems. For example, the condensation of the anthracenyl substituted unsaturated 1,4-dicarbonyl compound **24** with hydrazine gives the anthracenyl substituted pyridazine **25** (Scheme 1.9)³⁰.



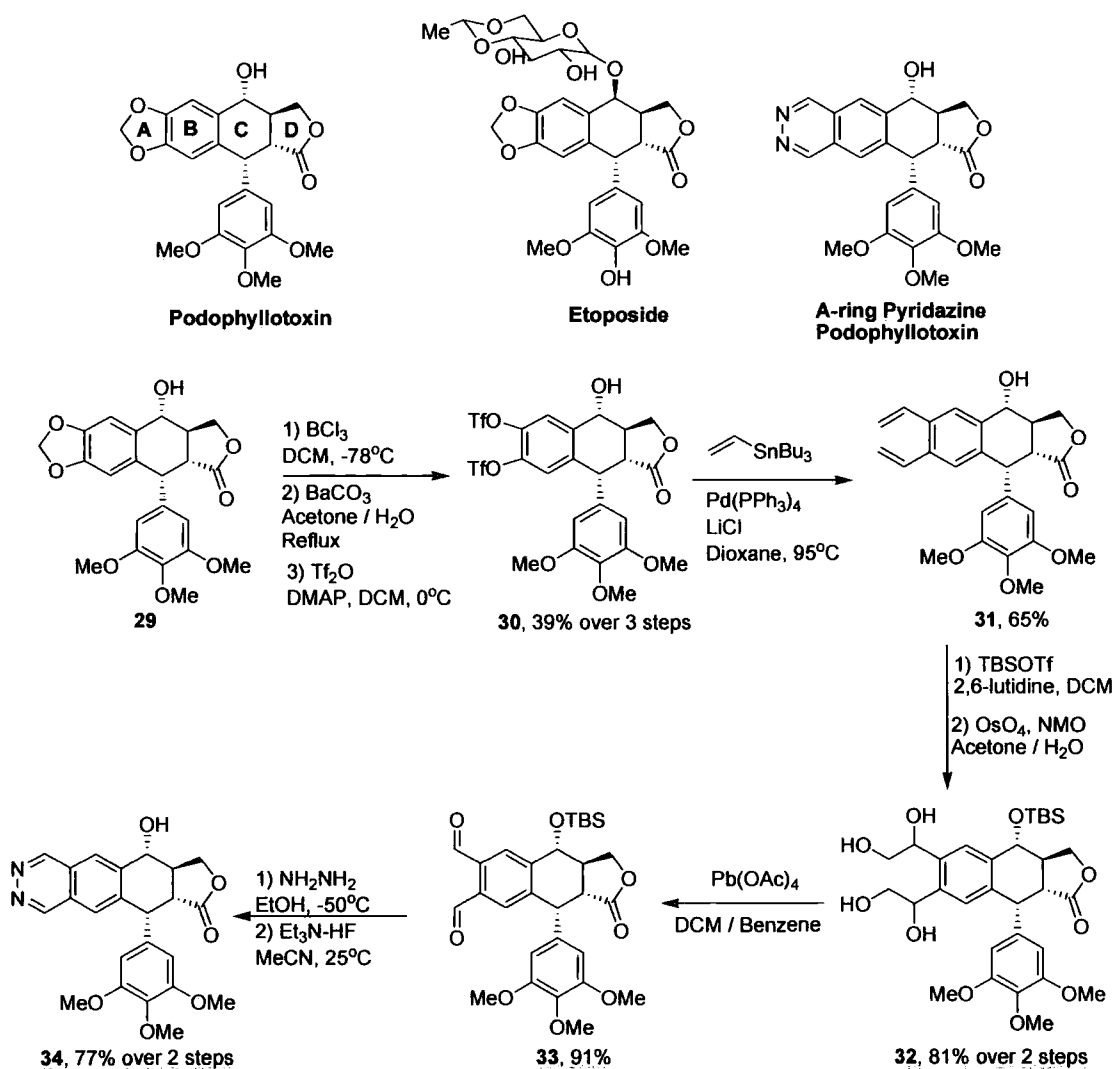
Scheme 1.9

Knochel *et al.* have developed the synthesis of functionalised α,β -dicarbonyl compounds *via* iodine-copper exchange of a vinylic iodide **26** followed by trapping with an acyl halide electrophile to yield a 1,4-unsaturated diketone **27**, which were condensed with hydrazine to yield polyfunctional pyridazine systems **28** in excellent yield (Scheme 1.10)³¹.



Scheme 1.10

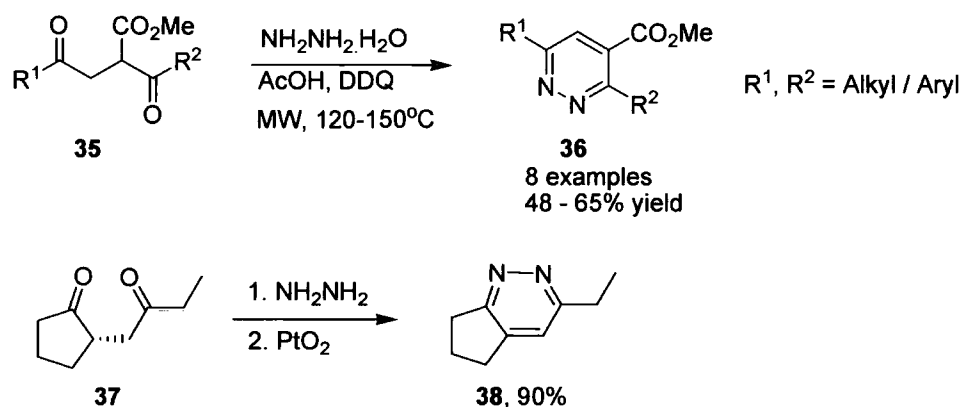
Aromatic systems substituted with carbonyl groups in an *ortho* relationship also possess an unsaturated 1,4-dicarbonyl structural motif, and, on reaction with hydrazine, yield pyridazines fused to an aromatic ring. A-ring pyridazine analogues of the natural products podophyllotoxin³² and etoposide³³ have been synthesised by this approach (Scheme 1.11). The natural product **29** is degraded using BCl_3 and BaCO_3 to hydrolyse the acetal subunit and the resultant diol is converted into the ditriflate **30**. Stille coupling using a vinyl tin reagent yields a dialkene **31**, which is doubly dihydroxylated using OsO_4 / NMO. Each diol is then oxidatively cleaved using lead tetraacetate to furnish the required *ortho*-dialdehyde **33** which yields the desired pyridazine analogue **34** on condensation with hydrazine and appropriate deprotection.



Scheme 1.11

Saturated 1,4-dicarbonyl compounds are much more accessible than their unsaturated counterparts and, consequently, have been more widely utilised in pyridazine synthesis. Their condensation with hydrazine necessarily affords a non-aromatic dihydropyridazine, which requires forcing conditions or the presence of an oxidant to achieve aromatisation.

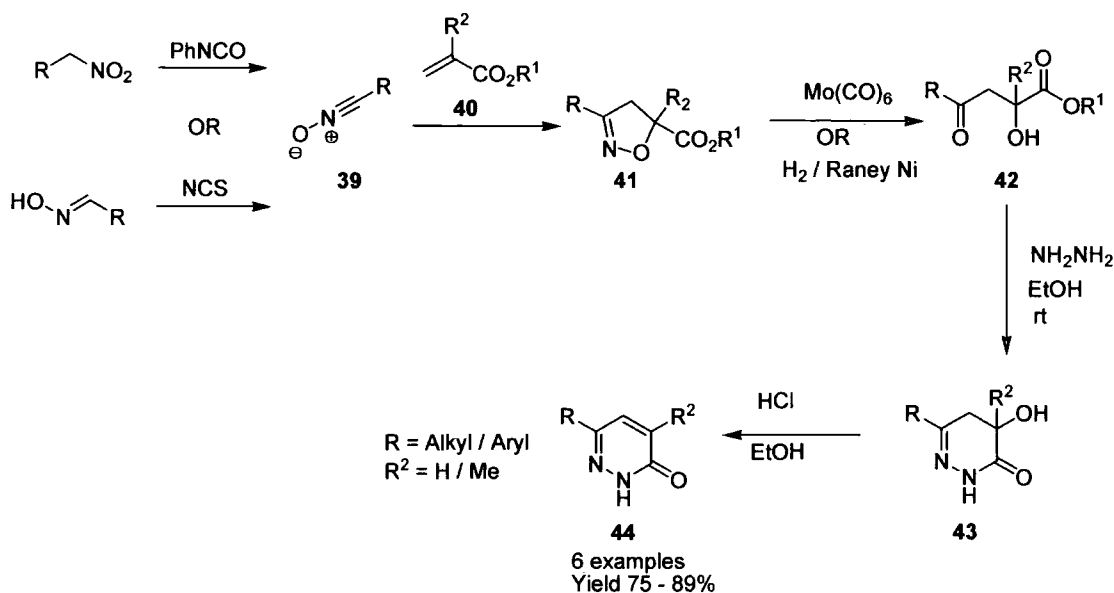
DDQ has been used as a common oxidant in the aromatisation of pyridazine derivatives formed from saturated 1,4-dicarbonyls, such as **35**. A one pot microwave assisted synthesis of pyridazine systems **36** has been developed using stoichiometric DDQ as oxidant (Scheme 1.12)³⁴. In the absence of DDQ a mixture of dihydropyridazine derivatives were obtained. Similarly, Nicolaou *et al.* have developed the use of PtO_2 as a mild oxidant for the synthesis of aromatic pyridazine derivatives **38**³⁵ from saturated dicarbonyl compounds **37**.



Scheme 1.12

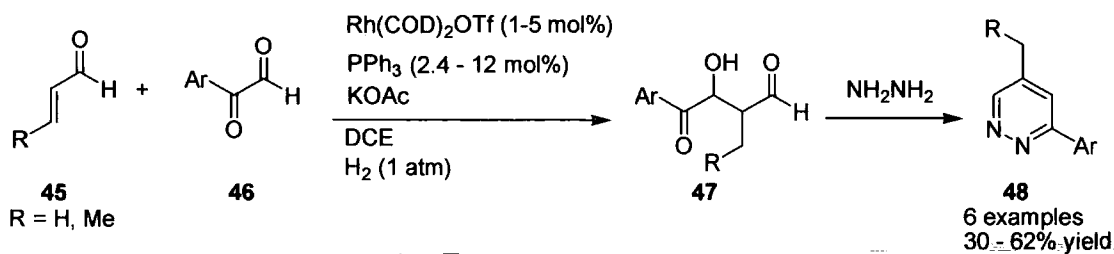
If a suitable leaving group can be introduced into a dihydropyridazine, then aromatisation can be achieved by elimination with no oxidation being required. This strategy was utilised in the synthesis of a small library of six substituted pyridazin-3(2*H*)-one analogues³⁶, in which the dihydropyridazin-3(2*H*)-one compounds produced were functionalised with a hydroxyl group as leaving group (Scheme 1.13). The required 1,4-dicarbonyl unit was assembled by the [3+2] dipolar cycloaddition of substituted nitrile oxide derivatives **39** with acrylate ester systems **40**. The resultant dihydroisooxazole **41** was ring opened using either molybdenum hexacarbonyl or catalytic hydrogenation, yielding a α -hydroxy- γ -keto ester **42** which was ring closed using hydrazine at room

temperature to give the 4-hydroxydihydropyridazin-3(2*H*)-one **43**. Elimination of water to yield the aromatised pyridazin-3(2*H*)-one **44** was then carried out by refluxing with dilute ethanolic hydrochloric acid.



Scheme 1.13

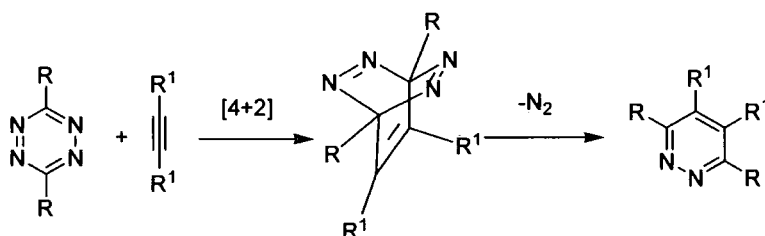
Similarly, 3,5-disubstituted pyridazines have been synthesised by a Rh catalysed reductive cross-aldolisation approach to the synthesis of β -hydroxy- γ -ketoaldehydes³⁷, again functionalised with a hydroxyl leaving group between the 1,4-dicarbonyl unit to allow aromatisation of the resultant dihydropyridazine by elimination (Scheme 1.14). An α - β unsaturated aldehyde **45** was reacted with a glyoxal derivative **46** in the presence of a Rh catalyst under a hydrogen atmosphere, with the active species being effectively a Rh enolate. The resultant 1,4-dicarbonyl compound **47** was then cyclised with hydrazine to yield an aromatic pyridazine derivative **48**.



Scheme 1.14

1.3.2 Cycloadditions of 1,2,4,5-Tetrazines

An alternative approach to the synthesis of pyridazine derivatives is *via* the cycloaddition of 1,2,4,5-tetrazines with suitable dienophiles³⁸, which is known as the Carboni-Lindsey reaction, discovered in 1959³⁹. It proceeds *via* a [4+2] cycloaddition of the 4π azadiene component of the tetrazine and a $2\pi_{\omega}$ dienophile component, producing a bicyclic intermediate that extrudes nitrogen to give the pyridazine product. For the synthesis of aromatic pyridazine systems an alkyne is required as dienophile, if an alkene derivative is used then a dihydropyridazine ring is formed, and a subsequent oxidation step is required to achieve aromaticity.



Scheme 1.15

Kinetic studies of the cycloaddition of alkynyl boronates with tetrazines have shown that it is *pseudo*-first order with respect to the tetrazine which is consistent with a concerted mechanism⁴⁰. Computational methods have been used to show that the cycloaddition process is indeed concerted and proceeds *via* an early, reactant-like transition state⁴¹ which is highly synchronous. The extrusion of molecular nitrogen from the intermediate is rapid and highly exothermic and the bicyclic intermediates have never been observed, so the rate determining step is therefore the formation of the intermediate.

This is an inverse electron demand Diels-Alder type reaction which is accelerated by the presence of electron withdrawing groups on the tetrazine and electron donating groups on the dienophile component. The key orbital interaction is between the LUMO of the diene and the HOMO of the dienophile. This has been supported by kinetic studies⁴², comparing reactivity of a range of alkenyl and alkynyl dienophiles with a 1,2,4,5-tetrazine diester. These results showed that the presence of electron withdrawing groups on the alkene can decrease rates of cycloaddition (Table 1.1). However, steric factors are also important, in that substituted alkenes were less reactive than unsubstituted ethylene. *Trans*-

alkenes were shown to be up to ten times more reactive than the equivalent *cis* alkene, as they are less sterically hindered. Alkynes are significantly less reactive dienophiles than alkenes.

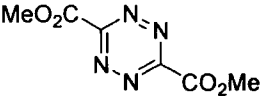

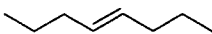

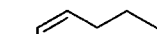


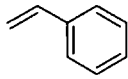
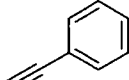
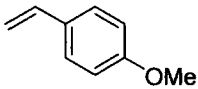
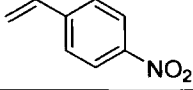
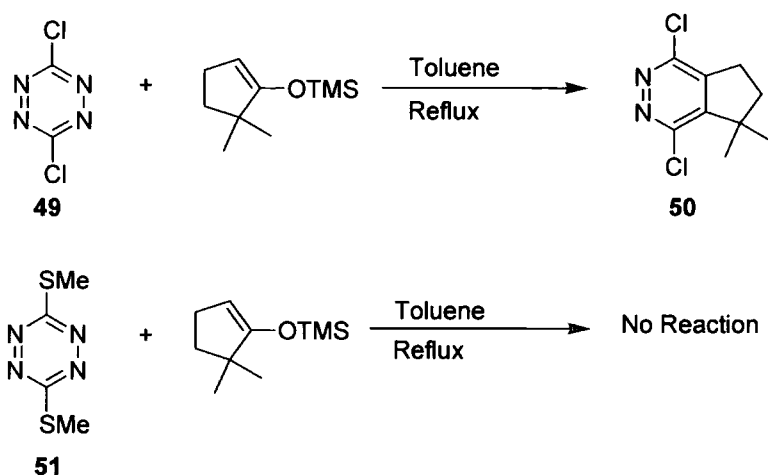
Rate of cycloaddition with			
Dienophile	$10^5.k_2[\text{dm}^3 \text{mol}^{-1} \text{s}^{-1}]$	Dienophile	$10^5.k_2[\text{dm}^3 \text{mol}^{-1} \text{s}^{-1}]$
	36300		330
	21700		48.4
	0.94		25.4
	6590		74
	25400		
	878		

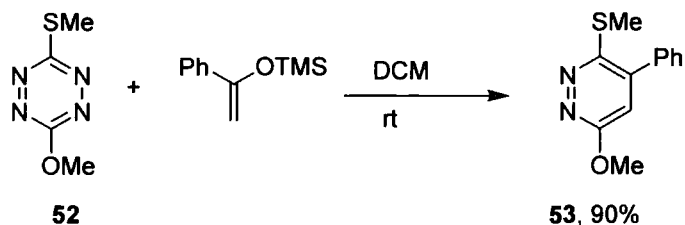
Table 1.1

Similarly, more electron deficient tetrazines are more reactive towards the cycloaddition process, for example, 3,6-dichloro-1,2,4,5-tetrazine **49** reacts efficiently with the silyl enol ether shown below (Scheme 1.16), whilst the more electron rich 3,6-(*bis*-methylsulfonyl)-1,2,4,5-tetrazine **51** is unreactive toward this dienophile⁴³. 3,4-(*Bis*(3,4-dimethoxybenzoyl)-1,2,4,5-tetrazine demonstrated limited reactivity towards electron deficient alkynes such as methyl propiolate, although this did require extended reaction times at high temperatures to achieve satisfactory conversion.



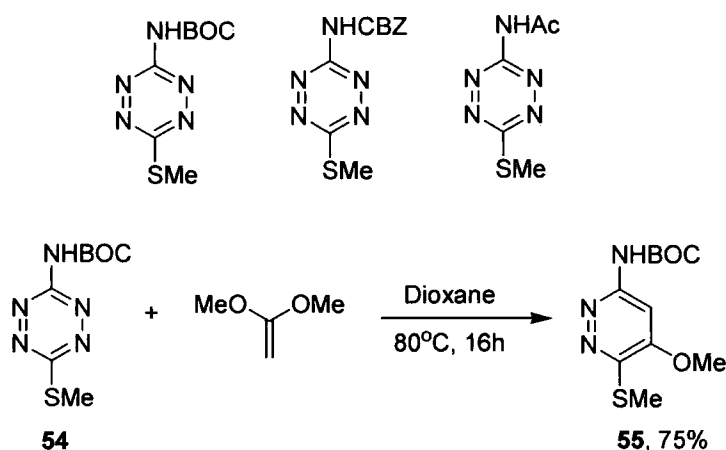
Scheme 1.16

More interesting is the chemistry of unsymmetrical tetrazine derivatives, as these present questions regarding the regioselectivity of the cycloaddition process. Unsymmetrical tetrazines can be prepared by nucleophilic displacement of the readily available 3,6-bis(methylthio)-1,2,4,5-tetrazine **51**, which is highly reactive towards nucleophilic displacement due to its four ring nitrogen atoms (c.f. the reactivity of diazines compared to pyridine). Thus, 3-methoxy-6-methylthio-1,2,4,5-tetrazine **52**, prepared by displacement of an SMe group with methanol in the presence of a catalytic amount of sodium methoxide⁴⁴, was reacted in cycloadditions with a range of enamines, enol ethers and alkynes (Scheme 1.17). The oxygen or nitrogen leaving group present on the enol ether or enamine enabled elimination to the aromatic pyridazine **53**. In the case of alkyne dienophiles, a 1:1 mixture of the two possible regioisomers was produced, but with 1,1-disubstituted enamines and enol ethers, cycloadducts were produced regioselectively.



Scheme 1.17

The study of regioselective cycloadditions of dienophiles to unsymmetrical tetrazines has since been extended by Boger, who has studied the cycloaddition reactions of *N*-acyl-6-amino-3-methylthio-1,2,4,5-tetrazines, such as **54**⁴⁵, which were found to proceed with excellent regioselectivity (Scheme 1.18).



Scheme 1.18

In general, this regioselectivity can be explained by consideration of electrostatic interactions, or by FMO theory (Figure 1.8). If electrostatics are considered, the electron rich terminus of the dienophile attaches itself to the most electron poor carbon of the tetrazine. Alternatively, overlap of the largest orbital coefficient in the HOMO of the dienophile and the LUMO of the tetrazine gives the same regioselectivity.

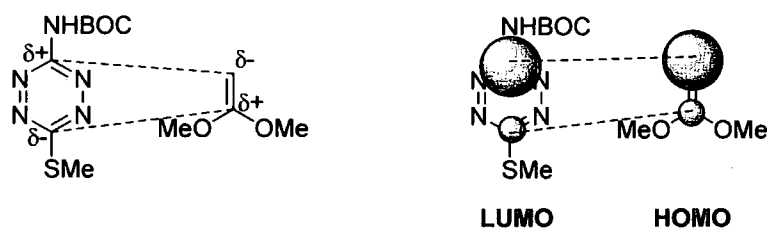
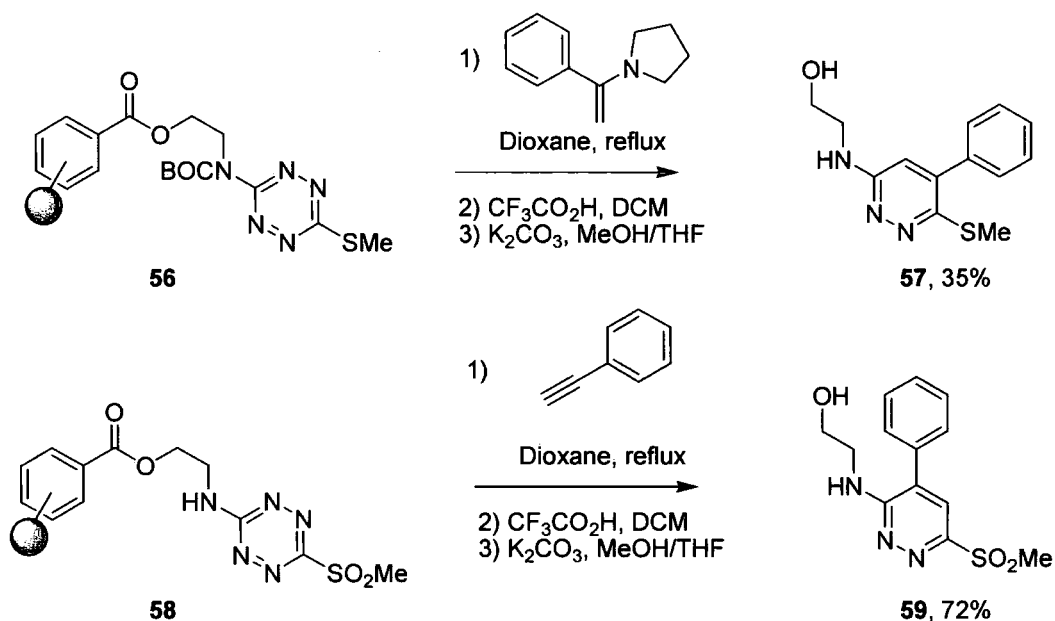


Figure 1.8

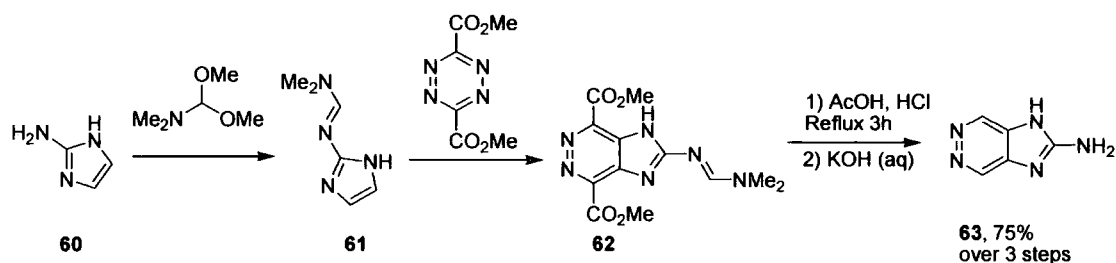
Solid supported tetrazines containing an amide linker to a solid support and sulfone or thioether substituents have been shown to undergo regioselective cycloaddition reactions with a range of alkene, enol ether and enamine dienophiles (Scheme 1.19)⁴⁶. An interesting ‘switch’ of regioselectivity is observed on oxidation of the thioether **56** substituent to the

sulfone **58**. This is because the electron withdrawing ability of the substituents is in the order $\text{SO}_2\text{Me} > \text{NBOC} > \text{SMe}$, so oxidation of SMe to SO_2Me reverses the regioselectivity of the process.



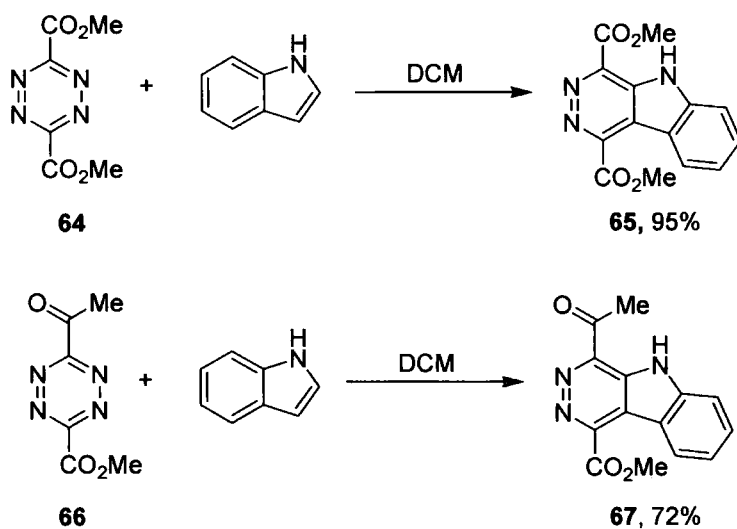
Scheme 1.19

Alternative dienophiles to alkynes and enamines that have been utilised include heteroaromatics such as imidazole or indole. Snyder has developed the chemistry of heteroaromatic dienophiles in cycloaddition processes, and, in a synthesis of the proposed structure of the natural product zarzissine, imidazole **61** was employed as a dienophile to give the fused imidazo-pyridazine **63** (Scheme 1.20)⁴⁷. The reaction occurred efficiently even at -78°C , confirming the reactive nature of imidazole as a dienophile, and the electron deficient nature of the tetrazine. The spectral data of this compound did not agree with that obtained from natural zarzissine and so the structure of the natural product is still unconfirmed.



Scheme 1.20

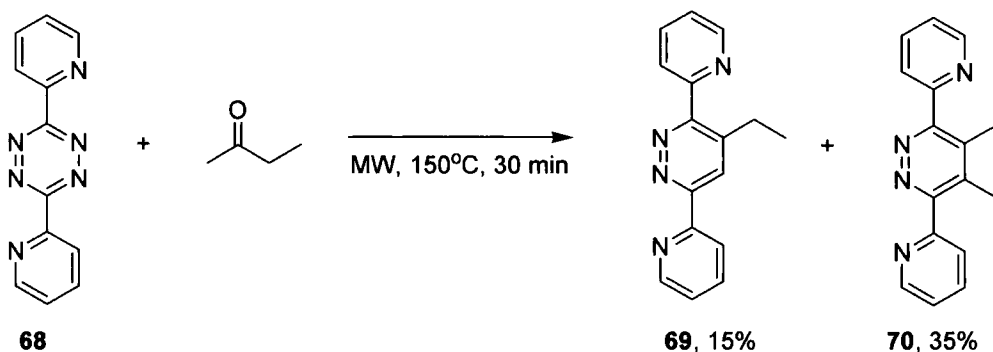
Indole is another heteroaromatic dienophile utilised in cycloaddition reactions. As part of a synthesis of staurosporine analogues the synthesis of various pyridazino[4,5-*b*]indole derivatives **65** and **67** were required. These were synthesised by an inverse electron demand Diels-Alder reaction of dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate **64** with indole (Scheme 1.21)⁴⁸. Similarly, the unsymmetrical tetrazine **66** undergoes regioselective cycloaddition with indole to give a single ring fused product⁴⁹.



Scheme 1.21

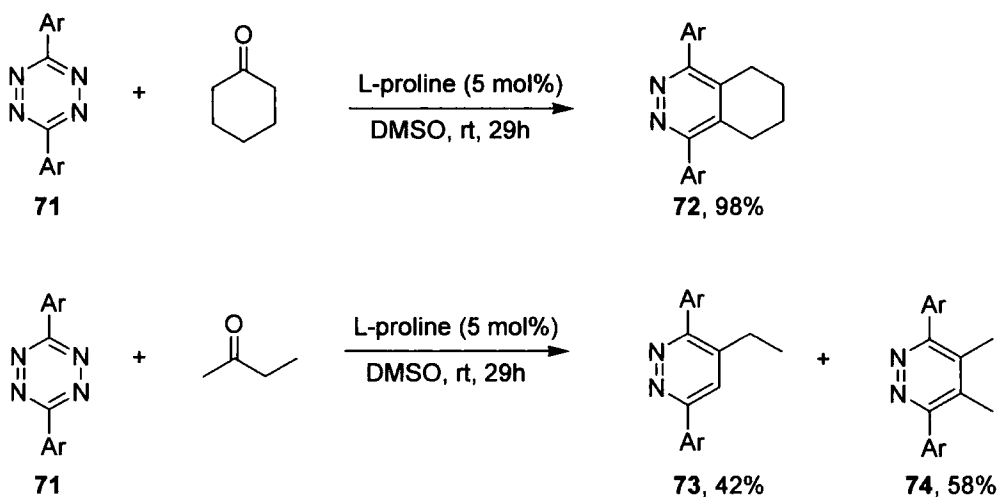
Ketones and aldehydes have also been shown to be effective dienophiles for related inverse electron demand Diels-Alder reactions with cycloaddition occurring *via* the enol tautomer. Various ketones and aldehydes have been reacted under microwave irradiation with 3,6-di-(pyridin-2-yl)-1,2,4,5-tetrazine **68** to yield substituted pyridazine systems (Scheme 1.22)⁵⁰. The high temperatures and pressures encountered in microwave conditions cause a shift in the keto-enol equilibrium towards the enol tautomer, increasing

the efficiency of the reaction. However, in many cases, two possible enol isomers are obtained, leading to a mixture of cycloadducts **69** and **70**.



Scheme 1.22

Organocatalysis is an area of much current research, offering potential advantages over traditional metal catalysed reactions. A proline catalysed inverse electron demand Diels-Alder reaction of ketones with 1,2,4,5-tetrazine **71** has recently been developed (Scheme 1.23)⁵¹. A screen of conditions showed that 5 mol% proline in DMSO was the best catalytic system and that the catalytic cycle occurred *via* the enamine. Again, in the case of unsymmetrical ketones, two possible enamines may be formed, so a mixture of regioisomeric pyridazines **73** and **74** are obtained.



Scheme 1.23

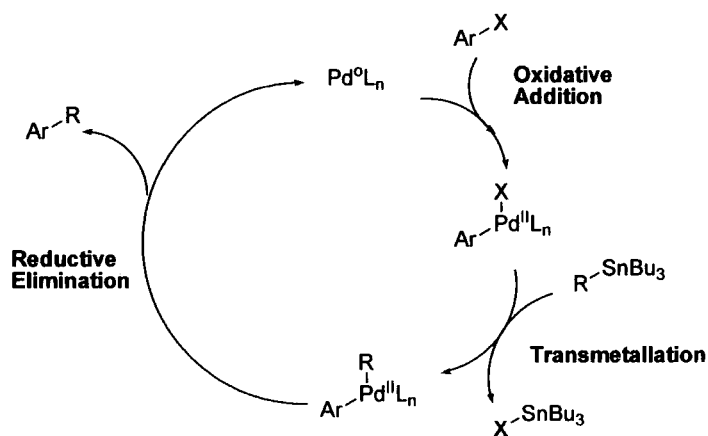
1.4 Functionalisation of Pyridazine Rings

The above strategies for the synthesis of pyridazine rings are useful but they can be limited if the introduction of a diverse range of substituents is required, for example in a medicinal chemistry development programme. Substituents are limited to those that can easily be introduced in the starting materials (1,4-dicarbonyl compound or tetrazine derivative and dienophile). Consequently, efficient synthetic routes are required for the rapid synthesis of a diverse range of heteroaromatic compounds such as pyridazine derivatives.

A better strategy for diversity oriented synthesis^{52, 53} is to functionalise a pre-formed pyridazine scaffold. Halo-pyridazine derivatives are often good precursors for these functionalisation approaches, which include nucleophilic substitution, palladium catalysed cross-couplings and metallation reactions. This section will describe the chemistry of pyridazines with respect to each of these functionalisation reactions.

1.4.1 Palladium Catalysed Cross-Coupling Processes

The chemistry of cross-coupling reactions is an area of much current interest, and can only be considered briefly here with regard to pyridazines. They involve the coupling of an aryl or vinyl halide with an organometallic under (typically) Pd(0) catalysis. The mechanism of cross-coupling processes is well established and is summarised below for the Stille reaction (Scheme 1.24)⁵⁴.



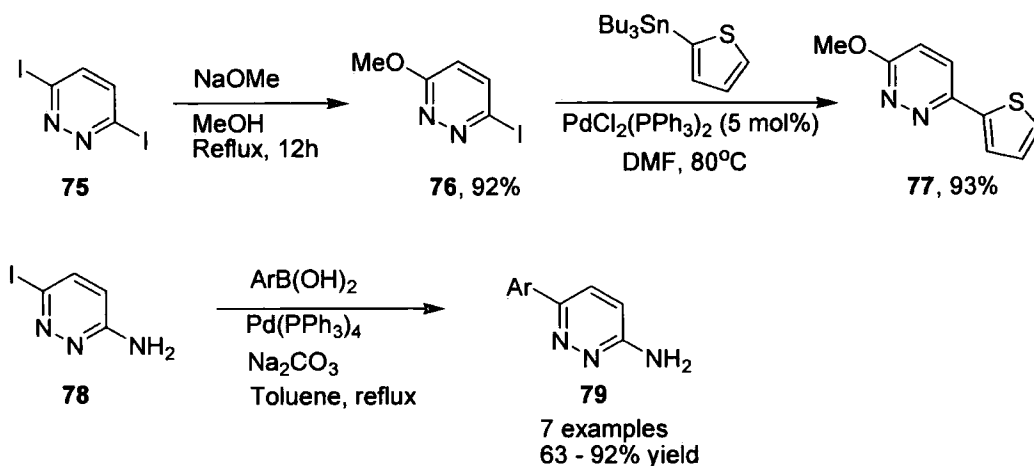
Scheme 1.24

The oxidative addition step is generally rate determining, and the ease of oxidative addition increases with decreasing C-X bond strength. Thus, the rate of oxidative addition generally increases in the order C-I > C-Br > C-Cl > C-F. Oxidative addition can be considered as a nucleophilic attack of the palladium complex on the aryl halide and, thus, is accelerated by the inclusion of electron-rich ligands on the palladium atom. Ligands that are commonly used in cross-coupling processes are typically phosphines such as PPh₃, PCy₃ and P^tBu₃, but more recently alternative ligands such as *N*-heterocyclic carbenes have been developed.

Transmetallation varies with the named cross-coupling process, and is possible for a range of metals including boron (Suzuki-Miyaura), tin (Stille), copper (Sonogashira), magnesium (Kumada) and zinc (Negishi).

The final reductive elimination step furnishes the desired coupled product and restores the catalyst. This step is accelerated in sterically crowded Pd complexes, so reductive elimination is assisted by bulky ligands.

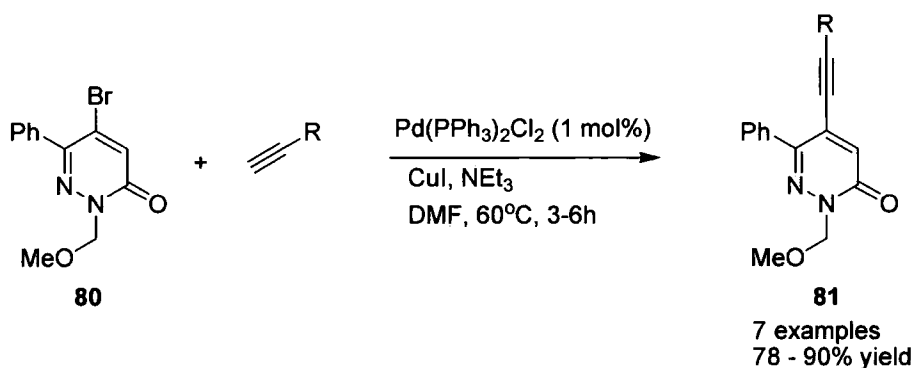
The palladium catalysed cross-coupling chemistry of pyridazines has been recently reviewed^{55, 56}, and is of much interest, particularly in the synthesis of aryl-pyridazines. For example the 6-substituted 3-iodopyridazines **76** and **78** were reactive in Stille⁵⁷ and Suzuki⁵⁸ couplings respectively to give biaryl products **77** and **79** (Scheme 1.25).



Scheme 1.25

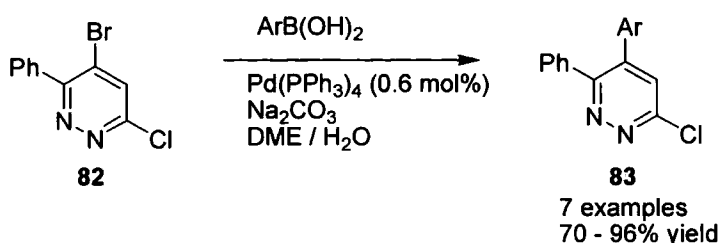
The chemistry of 5-bromo-6-phenylpyridazin-3(2*H*)-one has been extensively studied in Stille⁵⁹, Sonogashira⁶⁰ and Heck⁶¹ couplings (Scheme 1.26). For efficient

reaction of the parent pyridazin-3(2*H*)-one, the ring NH was protected as a methoxymethyl derivative **80**. Coupling with vinyl tin reagents proceeded in almost quantitative yield⁵⁹ whilst Sonogashira coupling with a range of alkynes was high yielding to give the heteroaryl-acetylene **81**⁶⁰. Heck couplings were more sensitive to conditions but the coupled products were obtained in moderate to good yield if the bulky phosphine P(*o*-tolyl)₃ was used as ligand⁶¹. The products of these reactions have shown interest as potential platelet aggregation inhibitors.



Scheme 1.26

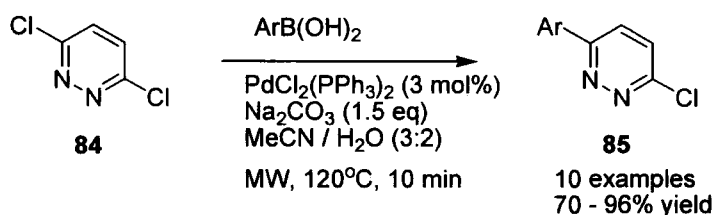
More interesting is the regioselective cross-coupling of polyhalogenated pyridazine systems⁶². For example, the greater reactivity of bromide compared to chloride in cross-coupling processes is demonstrated in the selective arylation of 4-bromo-6-chloro-3-phenylpyridazine **82** to give 4-aryl-6-chloro-3-phenylpyridazines **83** (Scheme 1.27)⁶³. Oxidative addition occurs selectively with a range of electron rich and electron deficient boronic acids at the weaker C-Br bond to give products arising from replacement of bromine.



Scheme 1.27

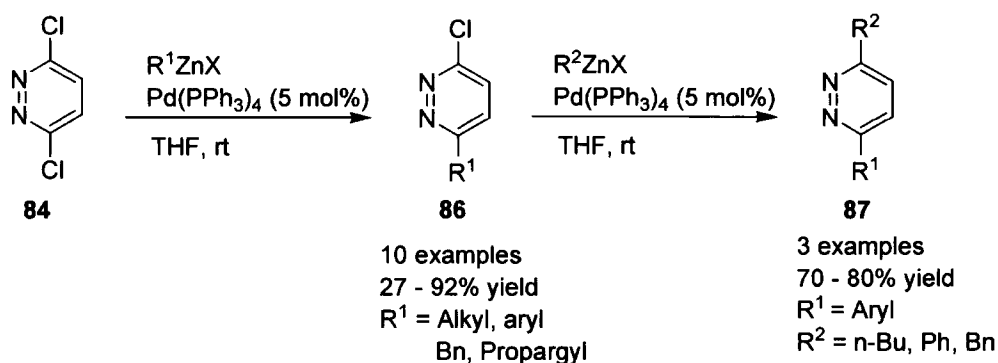
The cross-coupling of aryl chlorides is of much interest, as these are often more readily available than aryl bromides or iodides, yet the increased strength of the C-Cl bond means they are sometimes unreactive under standard conditions⁶⁴. In general, catalysts containing bulky, electron rich phosphines are required to assist the oxidative addition and reductive elimination steps. Both 3,6-dichloropyridazine and 4,5-dichloropyridazin-3(2*H*)-one are readily commercially available and have been utilised in cross-coupling processes⁶⁵.

3,6-Dichloropyridazine **84** could be selectively mono-arylated using 1.2 equivalents of boronic acid under microwave irradiation conditions⁶⁶ (Scheme 1.28). Optimisation of conditions showed the most effective catalyst to be Pd(PPh₃)₂Cl₂ (3 mol%) in acetonitrile / water (3:2) with Na₂CO₃ as base. Coupling with a range of boronic acids furnished the mono-arylated product **85** in good yield and the remaining chlorine atom could be displaced by a range of amines. With particularly electron rich boronic acids, such as 4-*t*-butylphenyl and 2-methoxyphenyl boronic acids, yields were reduced due to the formation of some disubstituted product.



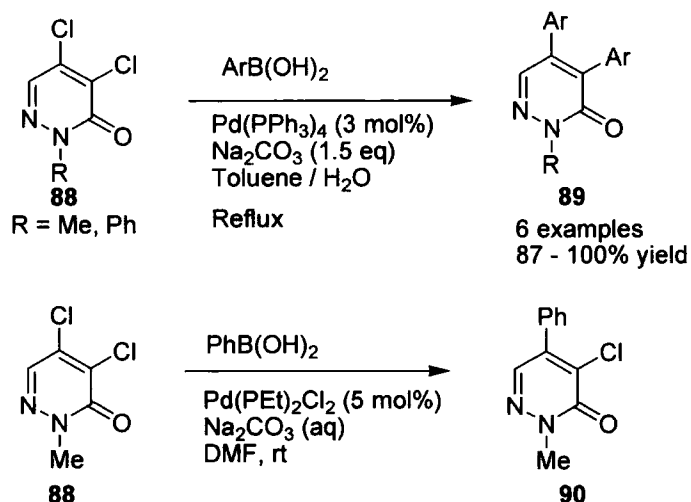
Scheme 1.28

Similarly, utilisation of 3,6-dichloropyridazine **84** in Negishi couplings with aryl and alkyl zinc derivatives gave the monosubstituted products **86** selectively (Scheme 1.29)⁶⁷. A second coupling with an organozinc compound yielded unsymmetrical 3,6-disubstituted pyridazines **87**.



Scheme 1.29

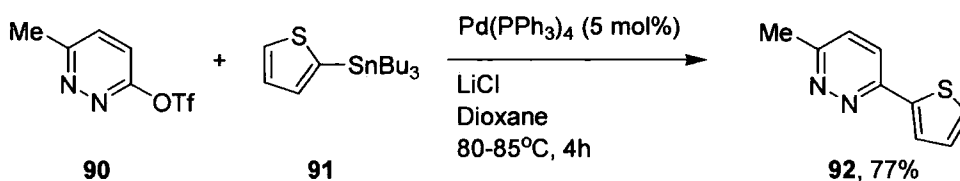
4,5-Dichloropyridazin-3(2*H*)-one **88** has been utilised in Suzuki^{68, 69}, Stille⁶⁹ and Sonogashira⁷⁰ couplings with excess boronic acid or alkyne to give disubstituted products **89** (Scheme 1.30). However, to minimise the formation of isomers in mono-coupling reactions of 4,5-dichloropyridazin-3(2*H*)-one, careful optimisation of conditions was required⁷¹. The catalyst that gave the best regioselectivity was found to be $Pd(PEt_3)_2Cl_2$, and, if reactions were run at room temperature in DMF, the 5-substituted isomer **90** was formed almost exclusively.



Scheme 1.30

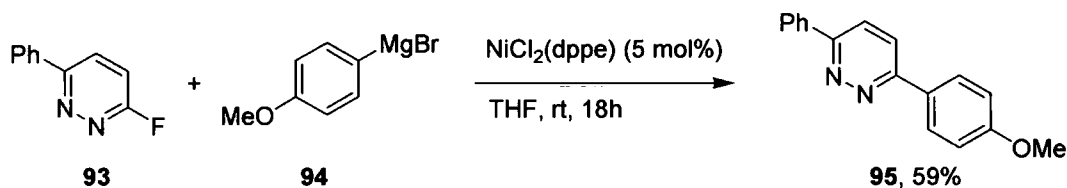
Pseudo-halides, such as aryl triflates or tosylates, can also be used as coupling partners in cross-coupling reactions. Trifluoromethanesulfonic acid 6-methyl-pyridazin-3-yl ester **90** was synthesised by reaction of 6-methylpyridazin-3(2*H*)-one with triflic

anhydride. The pyridazinyl triflate was then reacted with a range of aryl stannanes and boronic acids in Stille and Suzuki couplings⁷². Efficient reaction occurred with electron rich organometallics, such as the thiophene derivative **91**, although for electron poor organometallic systems, such as 2-pyridyl boronic acid, yields were poor.



Scheme 1.31

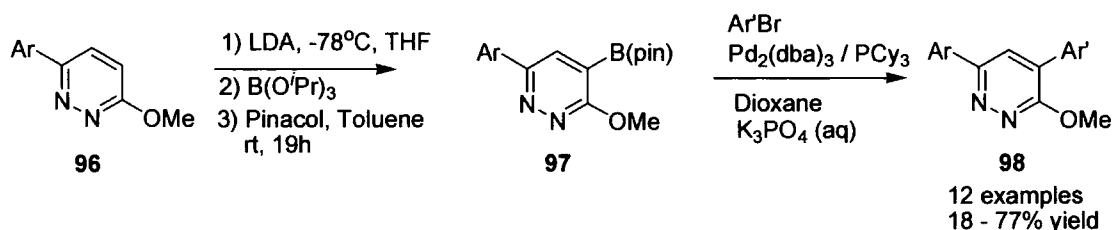
C-F activation is an area of current interest and, in general, is beyond the scope of this review. Only in recent years has the activation of strong C-F bonds become feasible with the development of highly active catalysts. A single application of C-F coupling has been applied to pyridazine derivatives; a Kumada-type coupling of an aryl Grignard reagent **94** and 3-fluoro-6-phenylpyridazine **93** using a nickel catalyst (Scheme 1.32)⁷³. Despite the appearance of this reaction as a simple nucleophilic substitution, the uncatalysed process did not proceed.



Scheme 1.32

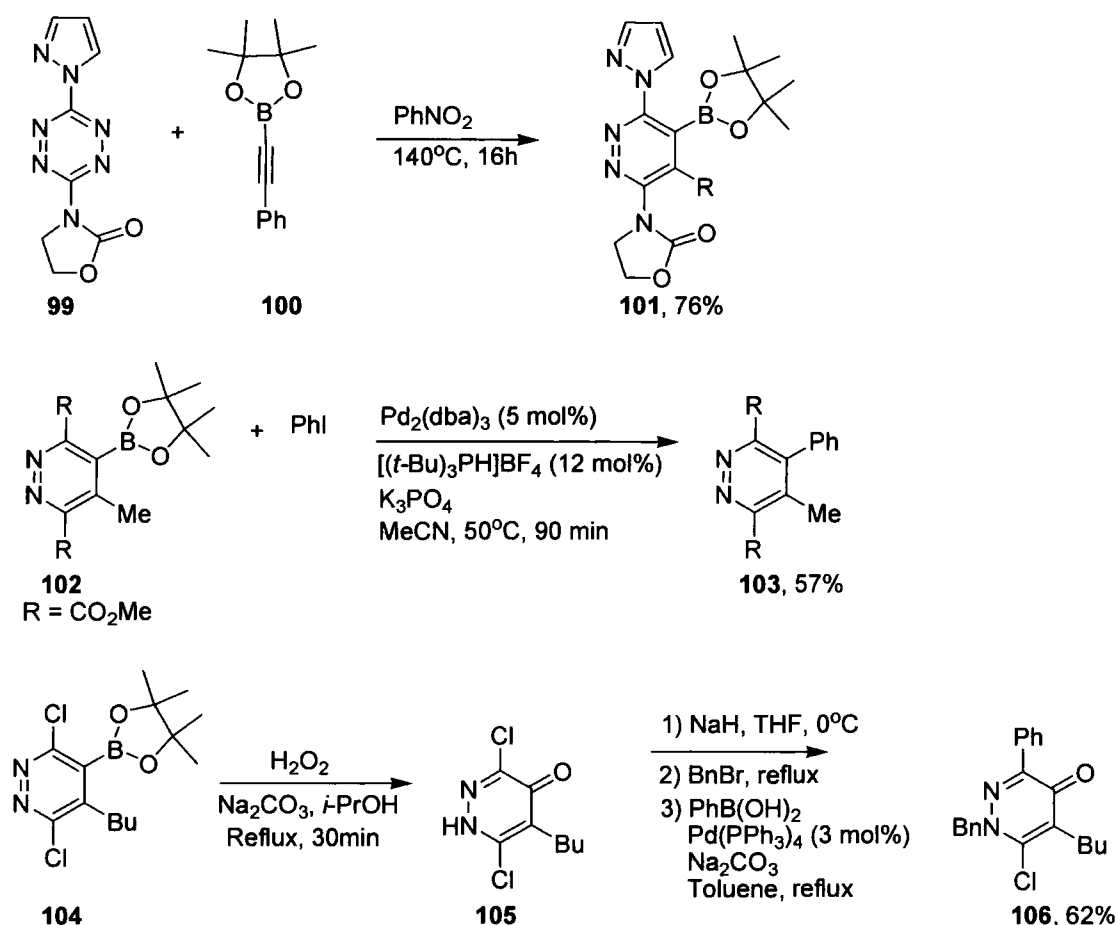
An alternative approach is the synthesis of organometallic pyridazines, such as pyridazinyl boronic acids, which can then be cross-coupled with aryl halides. The general approach to heteroaromatic boronic acids is by lithiation, followed by boronation. This approach has recently been utilised by Bryce *et al.* (Scheme 1.33), who synthesised a range of pyridazinyl boronic acids and their pinacol esters (which are more stable with respect to protodeboronation)⁷⁴. Lithiation occurred selectively adjacent to the directing methoxy group, followed by boronation with B(Oi-Pr)_3 and formation of the pinacol ester to give stable and isolable pyridazinyl boronic esters **97** which were then subjected to Pd catalysed

cross-coupling conditions to give a range of polysubstituted pyridazine systems **98** in moderate to good yield.



Scheme 1.33

A novel approach to the synthesis of pyridazinyl boronic ester derivatives has been taken by Harrity *et al.* who utilised the aforementioned Carboni-Lindsey cycloaddition of a 1,2,4,5-tetrazine with alkynyl boronic esters **100** (Scheme 1.34)^{75, 76}. Regioselective cycloadditions with unsymmetrical tetrazines **99** were developed. The pyridazinyl boronic esters produced could be functionalised by Suzuki coupling to give systems such as **103**, or by oxidation to the pyridazin-4(1*H*)-one **105**. Dichloropyridazinone systems were amenable to further diversification by regioselective Suzuki coupling as an approach to the synthesis of an array of pyridazinone derivatives **106**.



Scheme 1.34

Similarly, alkynyl silicon, germanium and tin reagents have been utilised in cycloaddition processes with 1,2,4,5-tetrazines to give organometallic substituted pyridazine systems^{77, 78}. Pyridazinyl stannanes were utilised in Stille couplings to give arylated products.

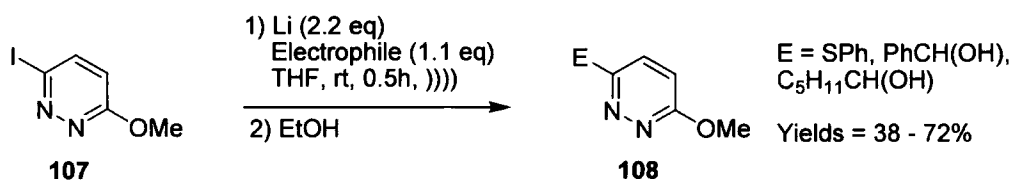
1.4.2 Metallation

The synthesis of functionalised pyridazine derivatives *via* metallated intermediates and trapping of the carbanion with electrophiles is a popular approach. Two strategies are commonplace; metal-halogen exchange⁷⁹ and metal-hydrogen exchange⁷⁹⁻⁸¹ and these will be considered in turn.

i) Metal-Halogen Exchange

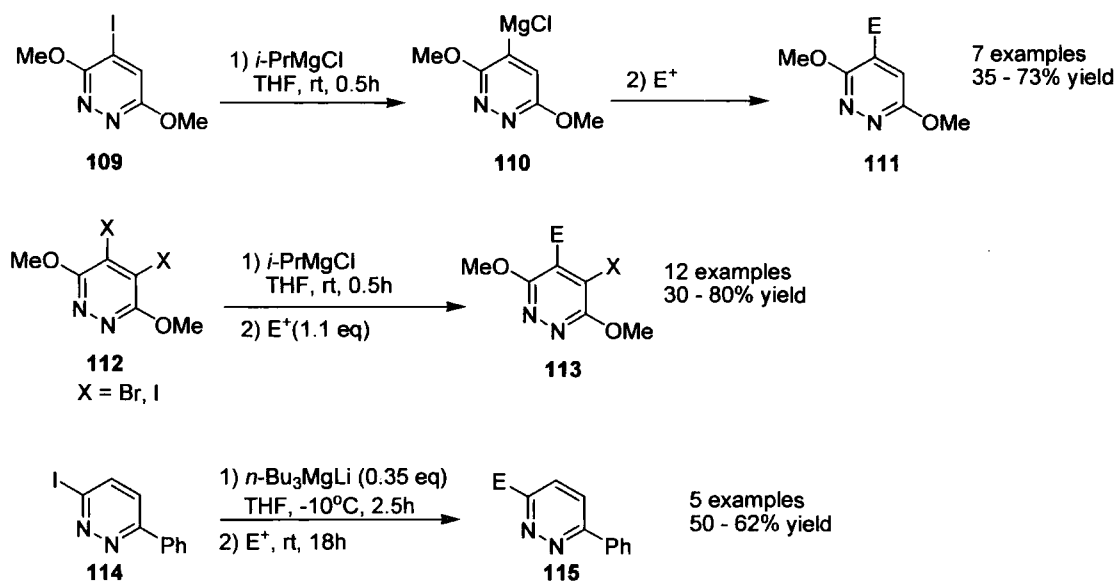
Examples of metal-halogen exchange are relatively rare on the pyridazine scaffold. Metal-halogen exchange generally proceeds much more rapidly than metal-hydrogen exchange, and is most effective on bromo- and iodo-heteroaromatics. The rate of metal-halogen exchange decreases with increasing C-X bond strength, so is extremely slow for C-Cl systems, and virtually unknown for C-F bonds.

Lithium-halogen exchange has been carried out on 4-iodo-3,6-dimethoxypyridazine and 3-iodo-6-methoxypyridazine **107** using lithium metal under sonication (Scheme 1.35)⁸². The heteroaromatic organolithium derivatives produced were trapped using a range of electrophiles including aldehydes and disulfides to yield substituted derivatives **108**.



Scheme 1.35

Magnesium-halogen exchange is also a synthetically useful process, and has been performed on pyridazine scaffolds using Grignard reagents, and also lithium tri-*n*-butylmagnesate (Scheme 1.36). Reaction of 4-iodo-3,6-dimethoxypyridazine **109** with *i*-PrMgCl gave the corresponding pyridazine Grignard reagent **110**, which was reacted with a range of electrophiles⁸³. Similarly, 4,5-diiodo-3,6-dimethoxypyridazine **112a** and 4,5-dibromo-3,6-dimethoxy-pyridazine **112b** could undergo selective mono-metallation to give monosubstituted products **113**⁸³ and 3-iodo-6-phenylpyridazine **114** underwent magnesium-halogen exchange with lithium tri-*n*-butylmagnesate⁸⁴. The organomagnesium intermediates are much more stable than their corresponding organolithium derivatives, so magnesium-halogen exchange reactions can be carried out at much higher temperatures.

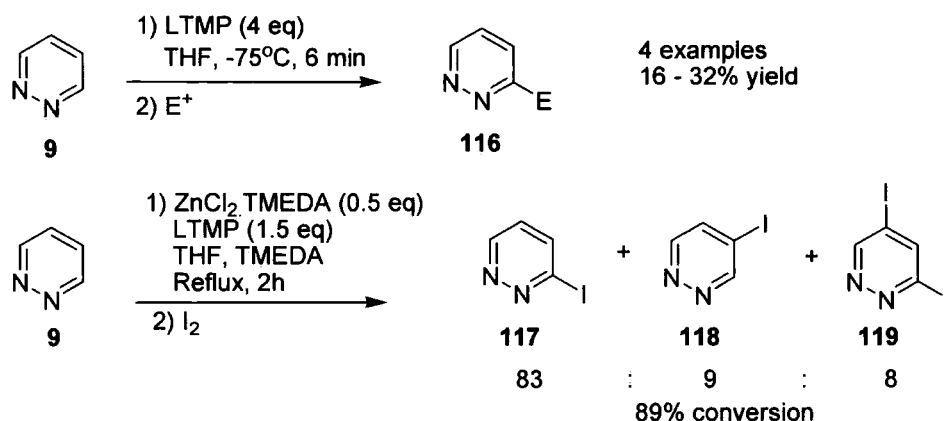


Scheme 1.36

ii) Metal-Hydrogen Exchange

Metallation by metal-hydrogen exchange is a much more common approach to the synthesis of functionalised pyridazine derivatives. The pK_a values of the two aromatic C-H bonds in pyridazine have been estimated to be 31.1 (*para* to ring nitrogen) and 37.9 (*ortho* to ring nitrogen)⁸⁵, therefore, strong organometallic bases, such as BuLi or LDA are required to achieve deprotonation. The site *ortho* to ring nitrogen is thought to be less acidic due to the electronic repulsion between the nitrogen lone pair and the carbanion that develops at the adjacent site.

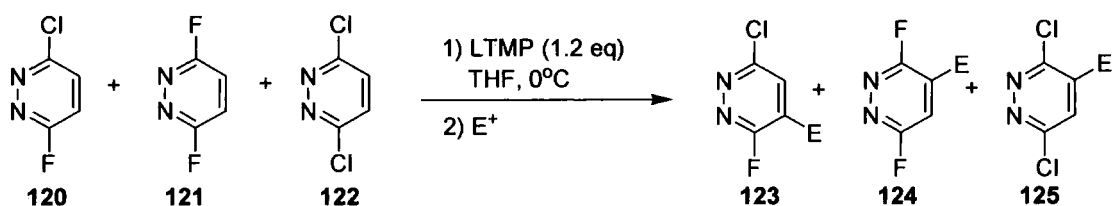
Lithiation of pyridazine **9** is possible using LTMP at -75°C (Scheme 1.37); this deprotonation occurs at C3⁸⁶ and this is likely to be due to coordination of the ring nitrogen to the lithium atom, directing deprotonation to the adjacent site, despite its lower acidity. Similarly, lithium mediated zincation of pyridazine proceeds mainly at C3 (**117**), with up to 20% competing zincation at C4 (**118**) depending on reaction conditions⁸⁷. A benefit of zinc-hydrogen exchange is the stability of the organozinc reagent which allows reactions to be performed at room temperature or higher.



Scheme 1.37

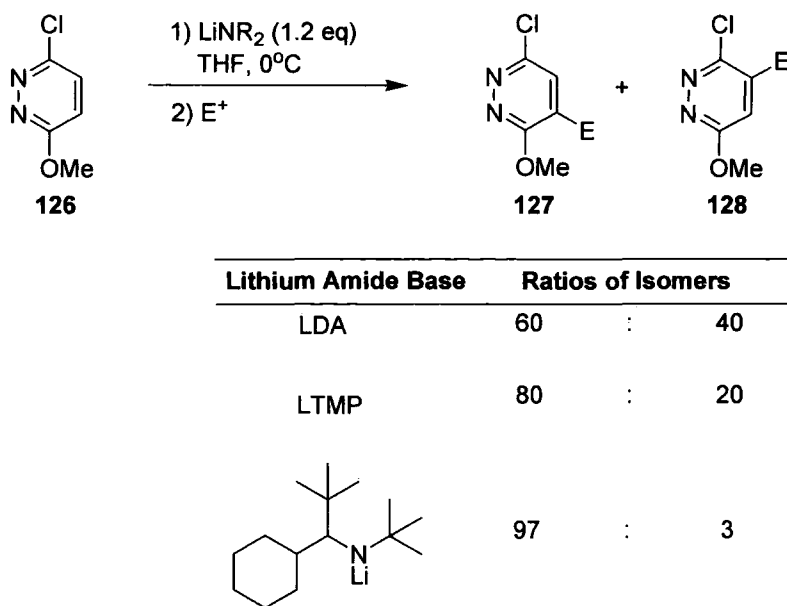
A popular recent approach is that of directed *ortho* metallation⁸⁸ (DoM), in which deprotonation is directed *ortho* to a ring substituent. Such directing groups (DMG = X, CF₃, OR, SR, S(O)R, SO₂R, NHCOR, CONHR) function either by stabilising an adjacent carbanion, for example, by an inductive or resonance electron withdrawing effect, or by coordinating to a lithium base, forcing deprotonation to occur at a neighbouring C-H bond.

Halogen atoms may be used as directed metallation groups (Scheme 1.38), for example, a mixture of three chloro-fluoropyridazines **120**, **121** and **122** each underwent metallation adjacent to a halogen substituent⁸⁹. 3-Chloro-6-fluoropyridazine **120** undergoes selective lithiation with LDA or LTMP *ortho* to the fluorine substituent to afford **123**, because fluorine is more able to stabilise an adjacent carbanion.



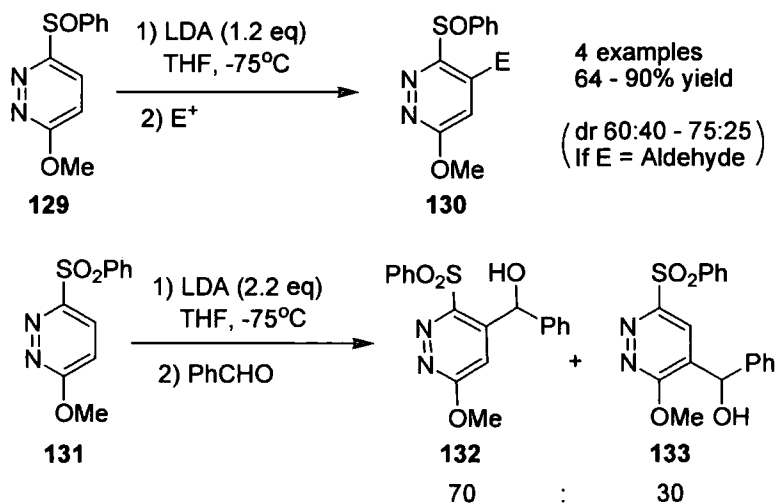
Scheme 1.38

The use of ether functionalities as directing metallating groups is also commonplace (Scheme 1.39), such as in the lithiation of 3-chloro-6-methoxypyridazine **126**⁹⁰. Lithiation *ortho* to the methoxy substituent to produce **127** was favoured, particularly when the steric demand of the lithium amide base was increased. It has been estimated that the directing ability of an alkoxy substituent is intermediate between a fluorine and chlorine atom⁸⁹.



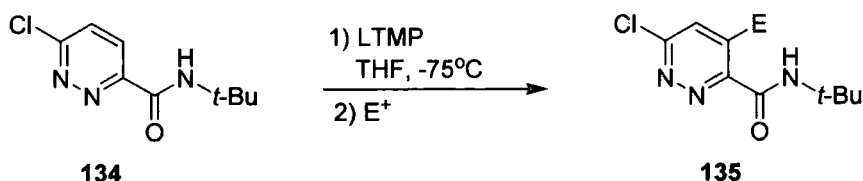
Scheme 1.39

Sulfur based DMGs include thioethers, sulfoxides and sulfones (Scheme 1.40)⁹¹. Lithiation of 3-phenylsulfinyl-6-methoxypyridazine **129** occurs adjacent to the sulfoxide substituent selectively⁹². If aldehydes were employed as the electrophile, two diastereoisomers were obtained with poor stereoselectivity. Sulfone directing groups **131** were slightly less effective, with a mixture of regioisomers **132** and **133** being obtained.



Scheme 1.40

Amides and thioamides have been shown to be particularly effective *ortho* directing groups (Scheme 1.41). Thus, 4-*N-tert*-butylpyridazinecarboxamide directs lithiation *ortho* to its amide substituent, and 3-chloro-6-*N-tert*-butylpyridazinecarboxamide **134** demonstrates that the *ortho* directing effect of an amide substituent is stronger than a chlorine atom⁹³.



Scheme 1.41

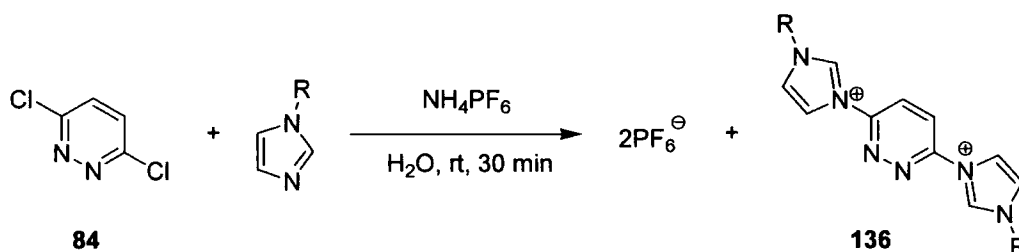
Therefore an approximate order of directing metallation group ability has been estimated to be $\text{CONR}_2 \sim \text{NRCOR} > \text{CN} \sim \text{SO}_2\text{R} \sim \text{S(O)R} > \text{OAr} > \text{OR} \sim \text{CF}_3 \sim \text{F} > \text{Cl}$ ⁸⁸. A more powerful DMG will direct substitution *ortho* to itself in the presence of a weaker DMG by more effectively stabilising an adjacent carbanion, or coordinating more strongly to an approaching lithium base.

Lithiation enables the reaction of a wide range of electrophiles with the pyridazine scaffold. However, its application in array and large scale synthesis may be limited by the low temperatures and inert atmosphere conditions required for its reactions.

1.4.3 Nucleophilic Aromatic Substitution

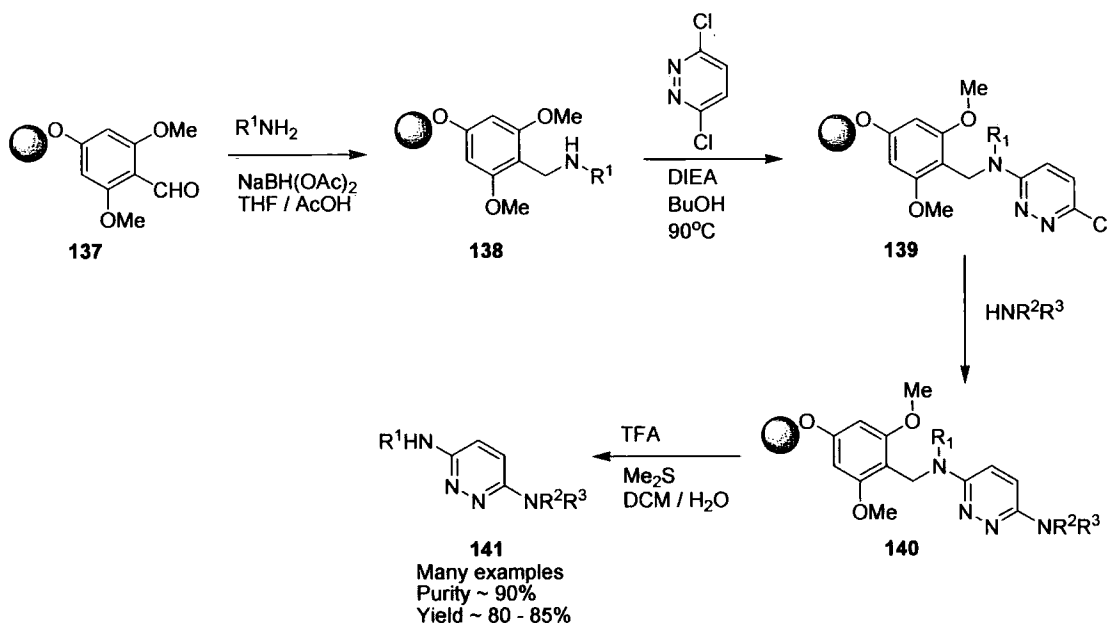
Nucleophilic substitution reactions of halopyridazine derivatives have been extensively studied, particularly for chlorinated systems. Suitable nucleophiles include amines, alkoxides, thiols and carbanion equivalents such as Grignard or organolithium reagents. 3,6-Dichloropyridazine and 4,5-dichloropyridazin-3(2*H*)-one have proven to be particularly popular substrates. The pyridazine ring system is activated at all ring sites by the presence of an *ortho*- or *para*-ring nitrogen, ensuring the majority of nucleophilic substitution reactions on this scaffold are efficient processes.

Reaction of 3,6-dichloropyridazine **84** with a range of *N*1-alkylimidazoles in excess yielded various bis(imidazolium) salts **136** with potential application as precursors to *N*-heterocyclic carbenes as ligands for catalysis (Scheme 1.42)⁹⁴.



Scheme 1.42

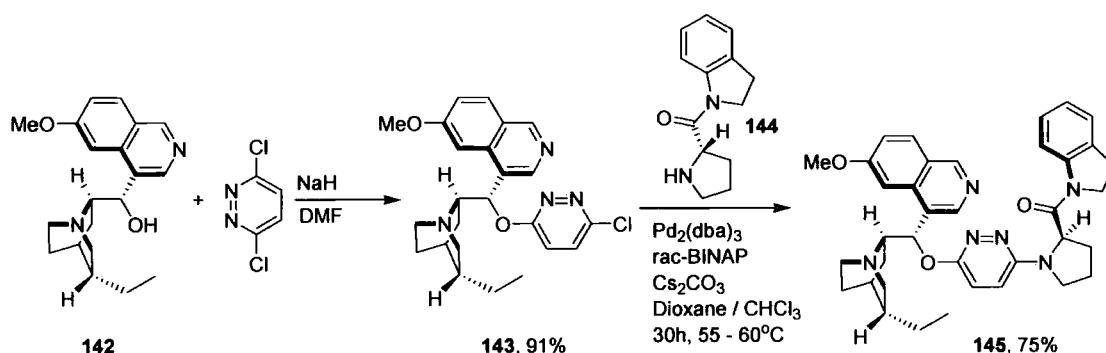
A combinatorial chemistry approach to the synthesis of disubstituted pyridazines was taken by Schultz *et al.* (Scheme 1.43)⁹⁵, who immobilised 3,6-dichloropyridazine on a solid support by reacting with various solid supported amines **138**, which were synthesised by reductive amination. The remaining chlorine atom could, in many cases, be displaced by reaction with amines, including anilines, which required the presence of a strong base such as KO^tBu . Cleavage from the resin using TFA / Me_2S gave an array of disubstituted pyridazines **141**.



Scheme 1.43

Corey has developed a pyridazine based catalyst for the enantioselective dihydroxylation of olefins starting from 3,6-dichloropyridazine (Scheme 1.44)⁹⁶. Nucleophilic displacement of one chlorine atom with the alcohol functionality of

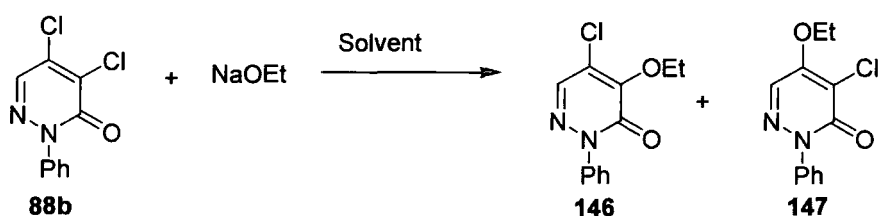
dihydroquinidine **142** in the presence of sodium hydride was followed by palladium catalysed displacement of the second chlorine with the proline based fragment **144**. The ligand **145** effected the dihydroxylation of alkenes in good yields (67 – 99%) and with a high degree of stereocontrol (e.e. 90 – 99%).



Scheme 1.44

Nucleophilic displacement reactions of 4,5-dichloropyridazin-3(2*H*)-one have also been examined and the presence of two chemically non-equivalent chlorine atoms in this system allow for two possible monosubstituted isomers to be produced upon reaction. Most interesting, particularly for an industrial setting where purification routes must be simple and efficient, are regioselective displacements, in which a single chlorine atom is substituted preferentially.

4,5-Dichloropyridazin-3(2*H*)-one demonstrates an interesting variation in regioselectivity in solvents of different polarity (Table 1.2)⁹⁷. In solvents of low dielectric constant (i.e. relatively non-polar), such as CCl₄ and THF, substitution occurs regioselectively at the 4-position, whilst in solvents of high dielectric constant (e.g. DMF, DMSO) substitution at the 5-position is preferred. In solvents of intermediate dielectric constant (e.g. *i*-PrOH, Acetone, MeCN), mixtures of isomers are obtained. Thus, a variation in reaction solvent polarity allows a simple regioselective route to both substituted isomers.



Solvent	Dielectric Constant, ϵ	Yield 4- isomer / %	Yield 5- isomer / %
CCl ₄	2.23	89	0
THF	7.32	87	0
EtOH	24.3	0	89
MeCN	36.2	36	53
DMF	36.7	0	88
DMSO	49.0	0	75

Table 1.2

Nucleophilic aromatic substitution approaches have been used extensively in the formation of ring fused systems and with fluorinated pyridazines, and these will be described in Sections 1.5 and 1.6.

1.5 Ring Fused Pyridazine Systems

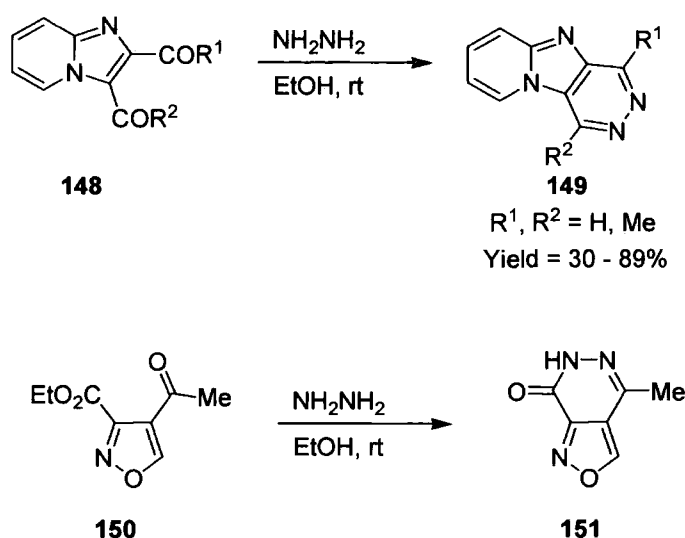
Ring fused pyridazines^{98, 99} have seen numerous practical applications, particularly in the synthesis of potential pharmaceutical products. The synthetic approaches outlined above for the synthesis of polyfunctional pyridazines are relevant to the synthesis of ring fused systems, and selected examples will be provided to exemplify these techniques.

1.5.1 Cyclisation Step Forms Pyridazine Ring

The first conceptual approach towards the formation of ring fused pyridazines is when the key ring-forming step also forms the pyridazine ring. Section 1.2 outlined the major routes for the formation of pyridazine rings: a) condensation of 1,4-dicarbonyl and hydrazine and b) inverse electron demand Diels-Alder reaction of 1,2,4,5-tetrazine and dienophile.

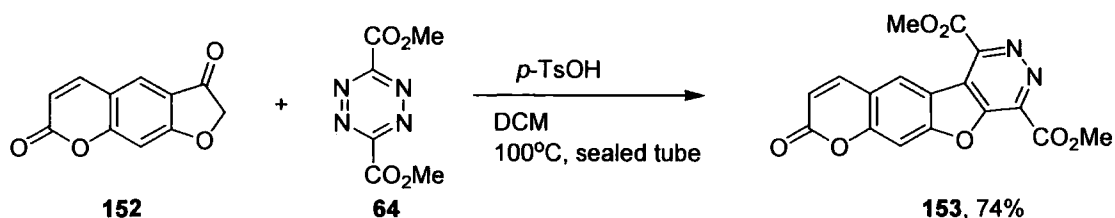
The reaction of cyclic 1,4-dicarbonyl compounds with hydrazine will yield a ring fused system (Scheme 1.45). For example, the *H*-imidazo[1,2-*a*]pyridine **148** functionalised

with two adjacent carbonyl groups was reacted with hydrazine to yield the tricyclic ring structure **149**¹⁰⁰. Similarly, the reaction of isoxazole **150** with hydrazine gave a isoxazolo[3,4-*d*]-pyridazin-7(6*H*)-one **151**, as an intermediate in the synthesis of potential PDE5 inhibitors¹⁰¹.



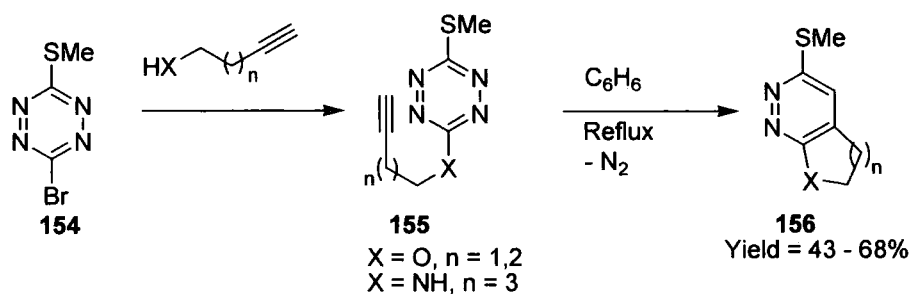
Scheme 1.45

The cycloaddition of 1,2,4,5-tetrazine derivatives with a suitable dienophile proceeds with extrusion of molecular nitrogen to yield pyridazine ring systems. The use of cyclic dienophiles such as indole⁴⁸ and imidazole⁴⁷ yield a ring fused pyridazine derivative. For example, cycloaddition of the enol tautomer of furocoumarin **152** with 3,6-bis(methoxycarbonyl)-1,2,4,5-tetrazine **64** yielded tetracycle **153** as a potential DNA intercalator (Scheme 1.46)¹⁰².



Scheme 1.46

Intramolecular inverse electron demand Diels-Alder cycloaddition of a tethered alkyne with a 1,2,4,5-tetrazine has also been shown to give ring fused pyridazines (Scheme 1.47). Nucleophilic attack of an alcohol¹⁰³ or amine¹⁰⁴ functionalised with a terminal alkyne on bromo-tetrazine **154** yields tetrazine **155**, functionalised with a side chain alkyne, which is capable of acting as an intramolecular dienophile. Cycloaddition yields a ring fused pyridazine derivative **156** on heating in refluxing benzene and five, six and seven membered fused rings have been synthesised in moderate to good yields.

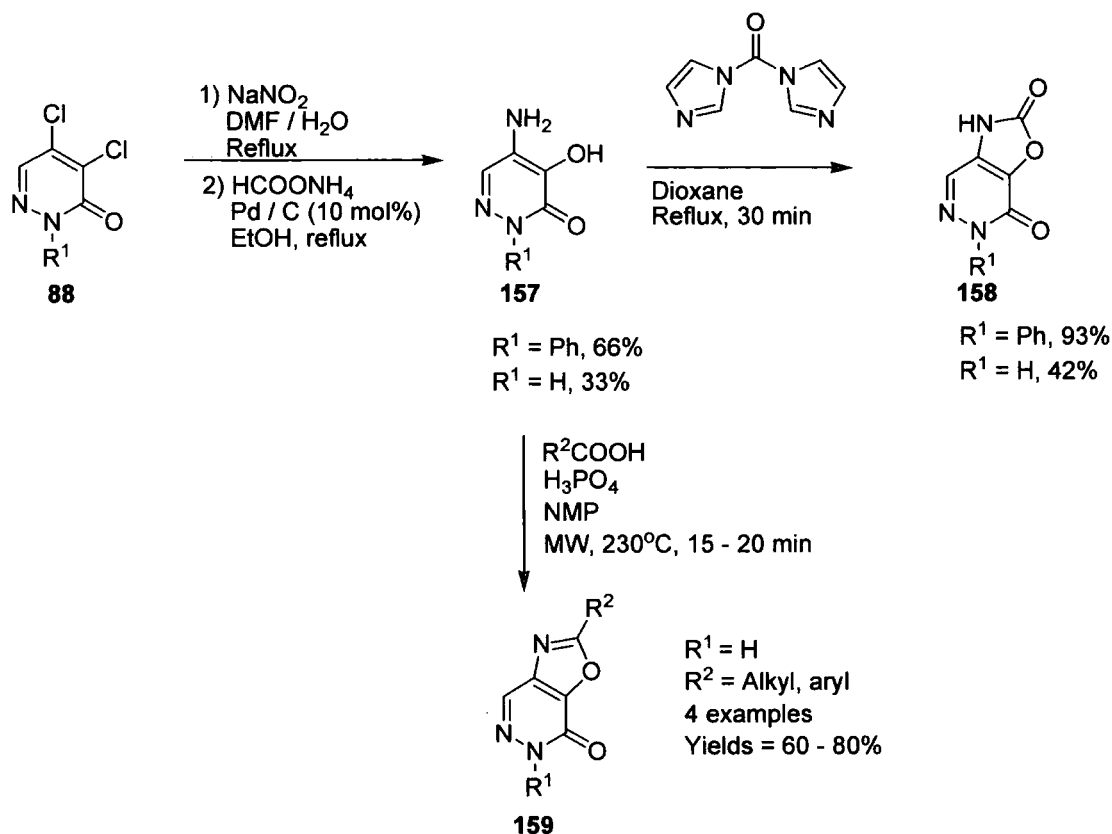


Scheme 1.47

1.5.2 Cyclisations of Suitable 1,2-Difunctional Pyridazines

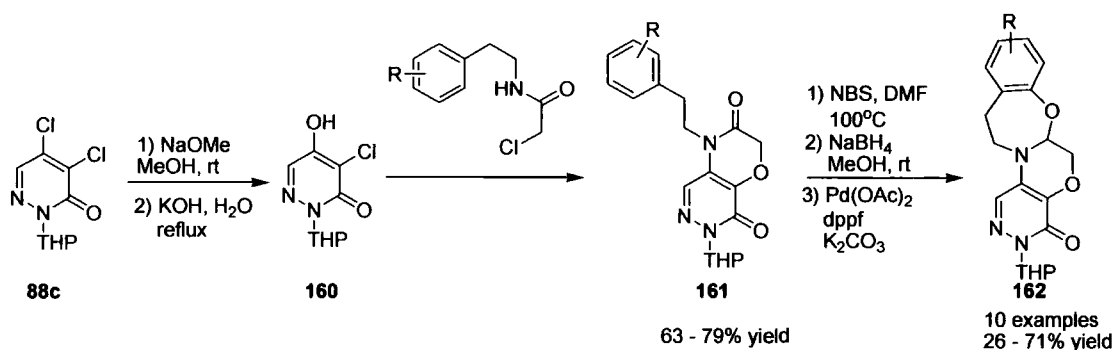
Difunctional pyridazines can be expected to react with suitable difunctionalised reagents to give cyclic systems. Such pyridazines may be functionalised with nucleophilic groups or suitable leaving groups to allow nucleophilic displacement.

Pyridazines functionalised with two adjacent nucleophilic groups (e.g. NRH, OH, SH) would be expected to react with suitable dielectrophilic species, such as carboxylic acid derivatives, to form cyclic products. For example, 5-amino-4-hydroxypyridazinones **157**, synthesised readily from 4,5-dichloropyridazin-3(2*H*)-one **88**, have been shown to react with 1,1'-carbonyldiimidazole to yield 1,3-oxazolo[4,5-*d*]-pyridazin-2(3*H*),7(6*H*)-diones **158** (Scheme 1.48)¹⁰⁵. The reaction was most efficient when the pyridazin-3(2*H*)-one ring NH was functionalised, such as with a phenyl group. Reaction with alkyl and aryl carboxylic acids yielded 1,3-oxazolo[4,5-*d*]-pyridazinones **159** via two successive condensation reactions.



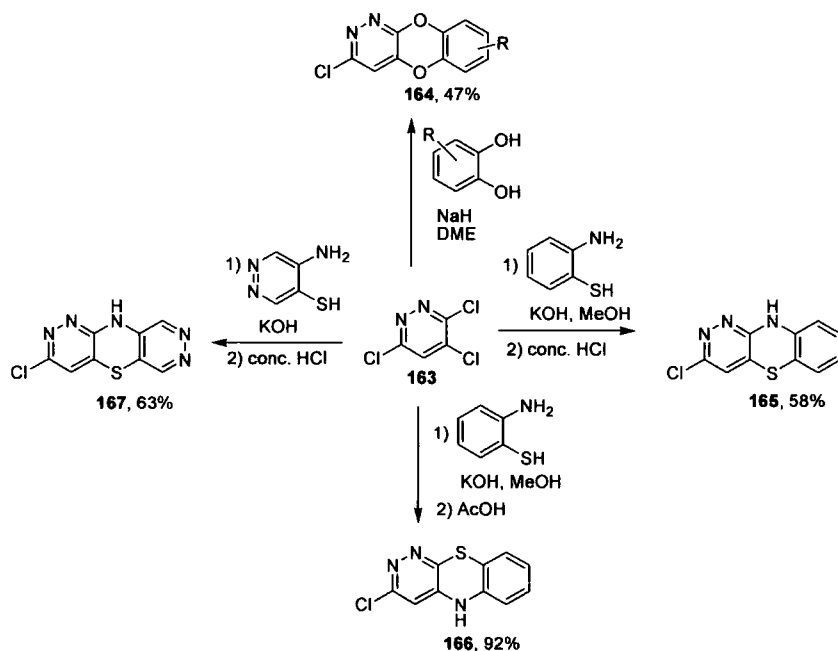
Scheme 1.48

A pyridazine ring functionalised with adjacent nucleophilic and electrophilic functionality would be expected to react with a tethered electrophile-nucleophile to yield a ring fused system. For example 4-chloro-5-hydroxy-2-(tetrahydro-2*H*-pyran-2-yl)-pyridazin-3(2*H*)-one **160** reacts with substituted phenylethyl-2-chloroacetamides *via* a Smiles rearrangement to yield [6,6] ring fused products **161** (Scheme 1.49). Bromination of the pendant phenyl ring, reduction of the lactam, followed by palladium catalysed C-O cyclisation yielded tetracyclic products **162** containing a seven membered oxazepine ring.



Scheme 1.49

A key aspect of this thesis is the reaction of dinucleophiles with polyhalogenated pyridazines. Reactions of suitable dinucleophiles, such as diamines, diols, amino-alcohols and amino-thiols, with 4,5-dichloropyridazine¹⁰⁶⁻¹⁰⁸, 4,5-dichloropyridazin-3(2*H*)-one^{106, 109-111} and 3,4,5-trichloropyridazine^{106, 112, 113} are known. As an example, the reaction of dinucleophiles with 3,4,6-trichloropyridazine **163**^{106, 114, 115} are shown in Scheme 1.50. Initial attack is likely to occur at the 4-position *para* to activating ring nitrogen, followed by cyclisation onto the adjacent chlorine atom. When amino-thiol derivatives were heated in the presence of weak acid (AcOH) Smiles rearrangement resulted in the production of a different regioisomer **166**.

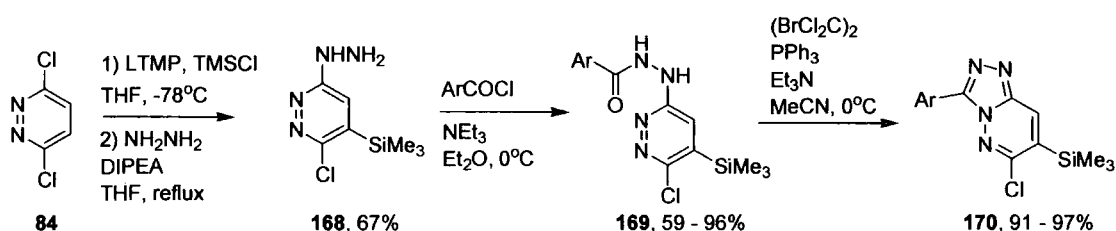


Scheme 1.50

1.5.3 Cyclisations Involving Pyridazine Ring Nitrogen

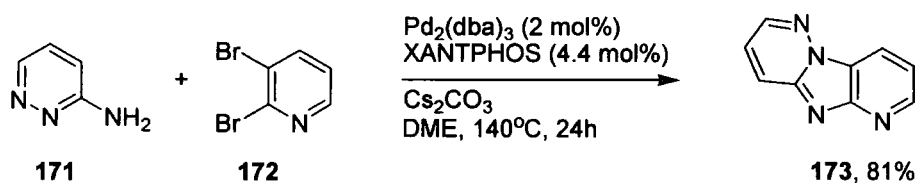
The ring nitrogen of a pyridazine is relatively nucleophilic and can therefore be utilised in reactions with electrophiles to form cyclic systems, particularly if there is some other functionality adjacent to ring nitrogen, to yield nitrogen-bridged products.

Cyclisation of a pyridazine ring nitrogen onto an adjacent hydrazide was achieved using triphenylphosphonium bromide in a Mitsunobu-type reaction to improve the leaving group ability of the oxygen (Scheme 1.51). The resultant 1,2,4-triazolo[4,3-*b*]pyridazines **170**¹¹⁶ were then further functionalised before biological screening as potential GABA_A receptor inhibitors.



Scheme 1.51

A regioselective Buchwald-Hartwig coupling reaction was utilised in the synthesis of novel tricyclic scaffolds **173** by reaction of 3-aminopyridazine **171** with 2,3-dibromopyridine **172** (Scheme 1.52)¹¹⁷. Initial coupling of the amino group occurred at C2 of the pyridine ring, whilst intramolecular C-N bond formation at the pyridazine ring nitrogen occurred at C3 to give a fused system.

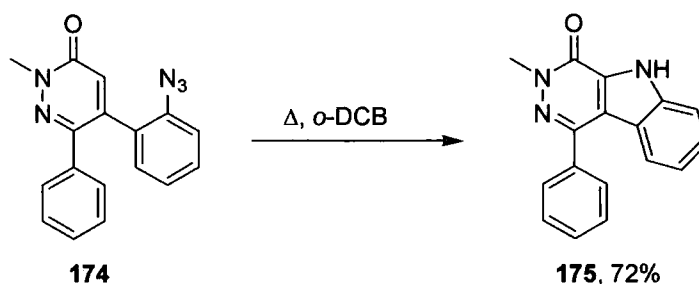


Scheme 1.52

1.5.4 Cyclisations onto Unfunctionalised Pyridazine Rings

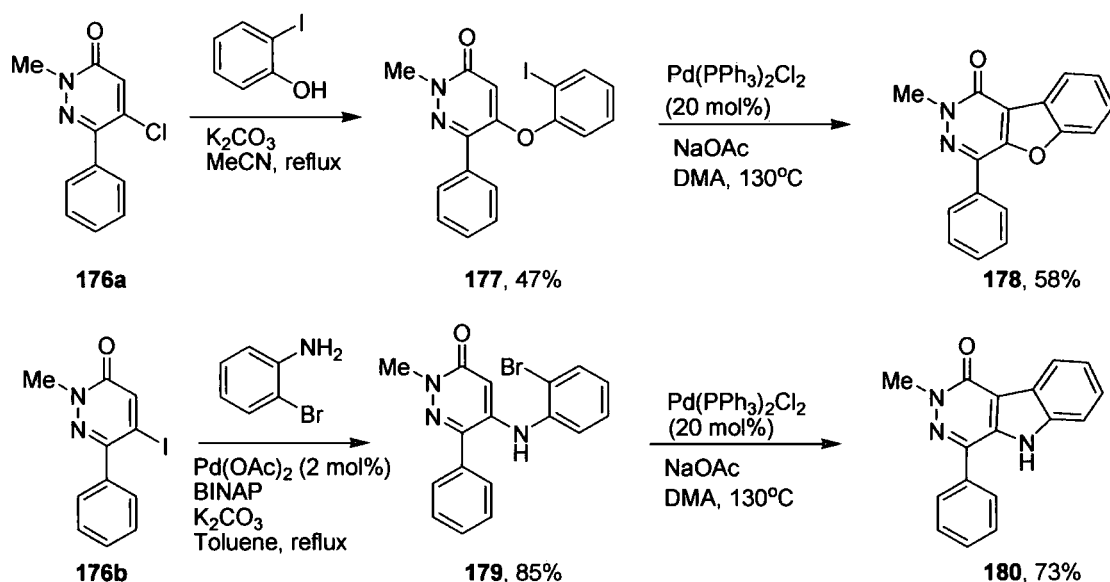
Although pyridazine rings are poorly reactive in electrophilic aromatic substitution processes, with highly reactive electrophiles such as nitrenes, or under palladium catalysis, such reactions become feasible for cyclisation processes.

The indolo-pyridazine scaffold **175** has been synthesised by nitrene insertion onto a pyridazine ring (Scheme 1.53)¹¹⁸. The action of heat on the aryl azide **174** led to the formation of a nitrene, with elimination of molecular nitrogen. This nitrene then underwent cyclisation onto the adjacent pyridazinone ring to form a fused system.



Scheme 1.53

Maes *et al.* also have developed a synthesis of 5*H*-pyridazino[4,5-*b*]-indoles and -benzofurans utilising an intramolecular Heck-type reaction as the key cyclisation step (Scheme 1.54)¹¹⁹. Nucleophilic substitution of 5-chloro-2-methyl-6-phenylpyridazin-3(2*H*)-one **176a** with *o*-iodophenol yielded **177**, which underwent palladium catalysed cyclisation onto the pyridazinone ring to furnish cyclic product **178**. However, high catalyst loadings of 20 mol% were required for effective cyclisation to occur. In the case of anilines, which were not sufficiently nucleophilic to attack the pyridazinone ring in the first step, palladium catalysed Buchwald-Hartwig amination was required to effect the initial substitution, which was followed by a second palladium catalysed cyclisation step under more forcing conditions to give the required 5*H*-pyridazino[4,5-*b*]-indoles **180**.



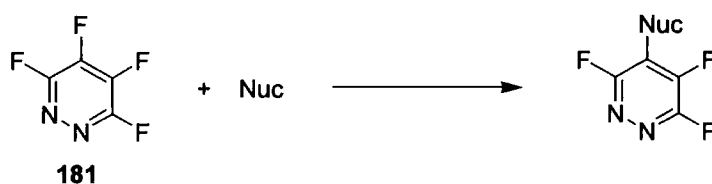
Scheme 1.54

1.6 Fluorinated Pyridazine Derivatives

A key focus of this thesis is the chemistry of tetrafluoropyridazine and its derivatives. Perfluoroheterocyclic chemistry has been extensively documented in theses of the Durham group, so just a brief introduction regarding the chemistry of tetrafluoropyridazine is appropriate here.

Perfluorination, that is fluorination at all available ring sites, of a six-membered heteroaromatic¹²⁰, dramatically increases the reactivity of the system towards nucleophilic substitution due to the high electronegativity of fluorine, which is the most electronegative element in the periodic table. The high strength of the C-F bond does not inhibit nucleophilic aromatic substitution to any significant degree, as the bond-breaking step is not rate-determining.

Tetrafluoropyridazine **181** has been shown to react selectively with a range of nucleophiles at the 4-position. The results are summarised in Table 1.3¹²¹⁻¹²⁹.



Nucleophile	Conditions	Yield / %	Reference
NaOMe	MeOH, 0°C	80	113
NH ₃	H ₂ O, 0°C	90	113
Et ₂ NH	NMP, 18°C	90	113
<i>n</i> -BuNH ₂	NMP, 20°C	84	114
PhNH ₂	NMP, 20°C	68	114
BnNH ₂	NMP, 20°C	36	114
	Sulfolane, 60°C	57	115
[†] CF ₃ CF ₂ ⁻	Sulfolane, 90°C	33	116
[†] (CF ₃) ₂ CF ⁻	Sulfolane, 10°C	35	117
[†] (CF ₃) ₃ C ⁻	Sulfolane, 20°C	80	118
[†]	Sulfolane, 20°C	87	119
[†] CF ₃ CF=CCF ₃ ⁻	Sulfolane, 105°C	5	120
[^] CF ₃ S ⁻	MeCN, 20°C	89	121

* Formed from reaction of reaction of perfluoro-1-methyl-1,3-diazacyclopent-2-ene and CsF

[†] Formed from reaction of perfluoroalkene / alkyne and CsF

[^] Formed from reaction of CF₂S and CsF

Table 1.3

Substitution at C4 is favoured for three key reasons: i) the activating influence of ring nitrogen *para* to the site of attack allowing delocalisation of the negative charge in the Meisenheimer intermediate onto the electronegative ring nitrogen; ii) C4 has the maximum number of activating *ortho*- and *meta*-fluorine atoms, which activate by inductive electron withdrawal from the site of attack; iii) the lack of a deactivating *para* fluorine atom.

Fluorine atoms *para* to a site of nucleophilic attack have been shown to be slightly deactivating¹³⁰⁻¹³². This is thought to be due to electronic repulsion between the fluorine lone pairs and the developing negative charge at the *para* carbon destabilising the transition state (Figure 1.9). *Ortho*-fluorine atoms have a similar deactivating effect on the Meisenheimer intermediate, however, this effect is outweighed by the inductive activation

on the initial state dramatically increasing the electrophilicity of the site of attack. Both initial-state effects and transition-state effects must be taken into account when considering the preferred site of attack on a perfluoroaromatic ring.

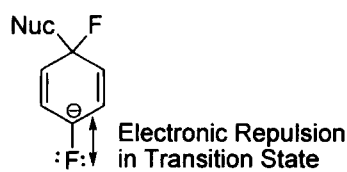
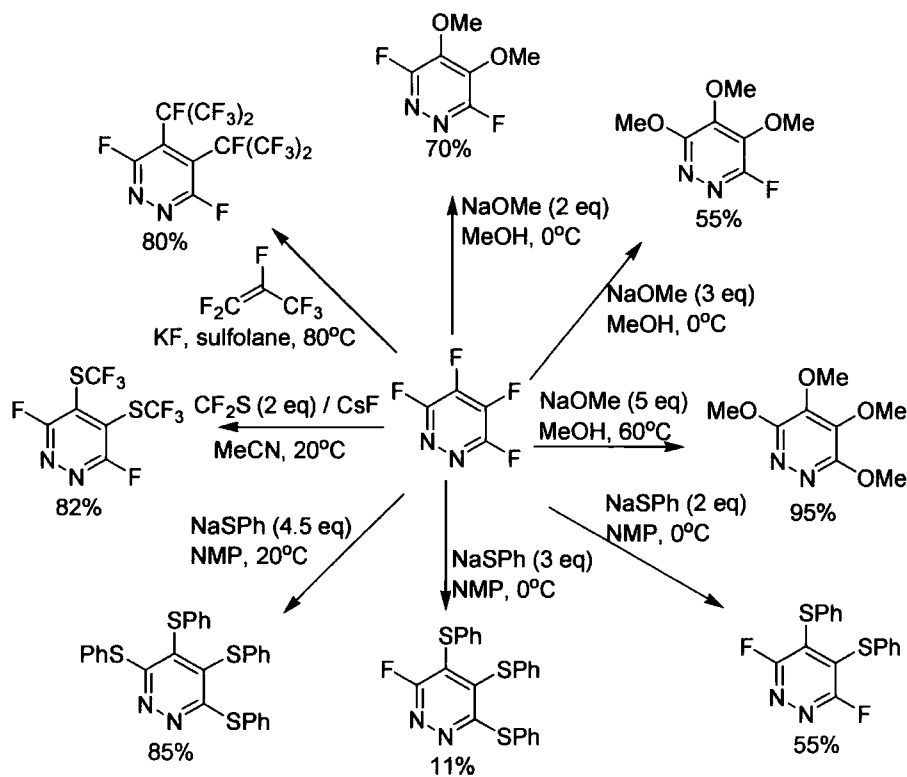


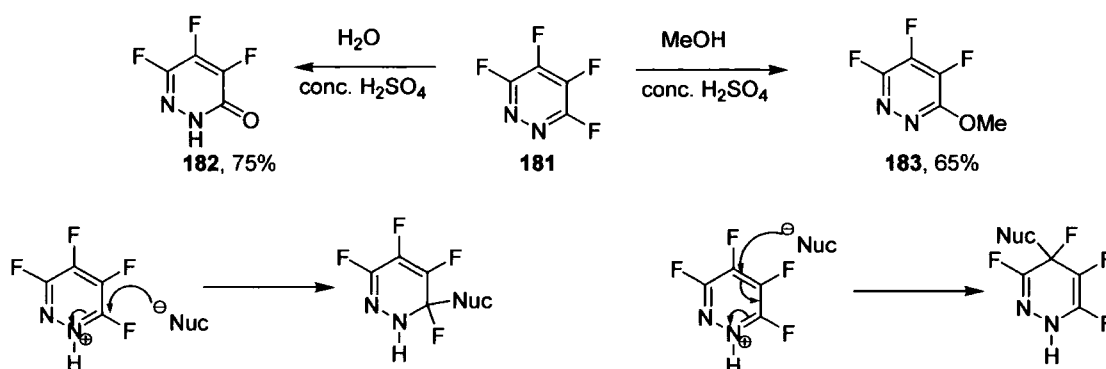
Figure 1.9

Polysubstitution reactions of tetrafluoropyridazine have been performed (Scheme 1.55), with di- and tri-substituted derivatives prepared using methoxide¹²¹, thiophenoxide¹²¹ and perfluoroalkyl anions^{123, 125, 129}. The second substitution has been shown in a few isolated cases to occur at C5, *para* to the second activating ring nitrogen. All four fluorine atoms have been successfully displaced under forcing conditions using sodium methoxide and sodium thiophenoxide¹²¹.



Scheme 1.55

Under strongly acidic conditions different regiochemistry is observed in nucleophilic aromatic substitution processes of tetrafluoropyridazine. Substitution of methanol in concentrated sulfuric acid occurs *ortho* to ring nitrogen to yield **183**, whilst acid hydrolysis gives 4,5,6-trifluoropyridazin-3(2*H*)-one **182**¹³³. These reactions are believed to proceed *via* the tetrafluoropyridazinium cation, and the selectivity can be explained because attack at C3 gives a more conjugated nucleophilic addition complex.



Scheme 1.56

However, to date, no nucleophilic aromatic substitution reactions of 4,5,6-trifluoropyridazin-3(2*H*)-one have been reported in the literature, so the factors determining regioselectivity of attack around this ring system are not established.

1.7 Fluorine in Medicinal Chemistry

The synthesis of polysubstituted derivatives from perfluorinated heteroaromatics should allow the incorporation of fluorine into these systems if not all fluorine atoms are displaced. Fluorinated compounds have been shown to have great application in the pharmaceutical industry, and it is thought that around 20 – 25% of drugs contain at least one fluorine atom¹³⁴. Examples of such fluorinated pharmaceutical products are shown in Figure 1.10 and include Cerivastatin, a pyridine-based drug, used in the treatment of atherosclerosis, Ciprobay, a quinolone antibiotic, Brequinar, an anti-tumour and an immunosuppressive agent and Prozac, a selective serotonin reuptake inhibitor, which can act as an anti-depressant by increasing the amount of serotonin in the brain.

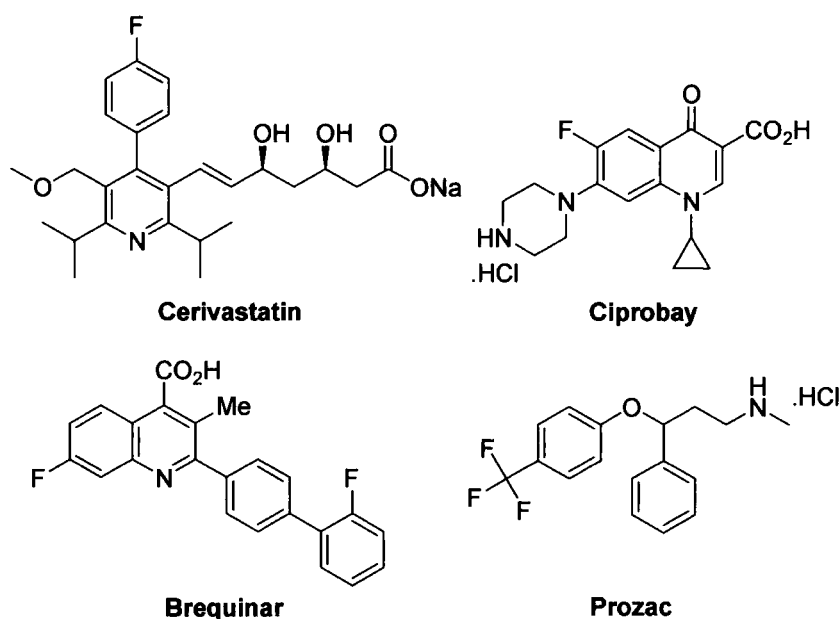


Figure 1.10

Fluorine can impart several advantageous properties on a potential drug candidate, and these effects are the focus of much recent study in an attempt to better understand the influence of fluorine incorporation on a range of properties.

1.7.1 Effects of Fluorine on Physicochemical Properties

i) pK_a

The introduction of a fluorine substituent can have a profound influence on the acidity or basicity of a molecule, due to its significant inductive electron-withdrawing effect. This effect is moderately predictable and changes in pK_a on increasing fluorination tend to be linear (Figure 1.11)¹³⁵. For example, the acidity of acetic acid derivatives is increased in a stepwise fashion on successive α -fluorinations. Similarly, the pK_{aH} of protonated β -fluorinated ethylamine derivatives decreases in an approximately linear relationship on increasing fluorine incorporation.

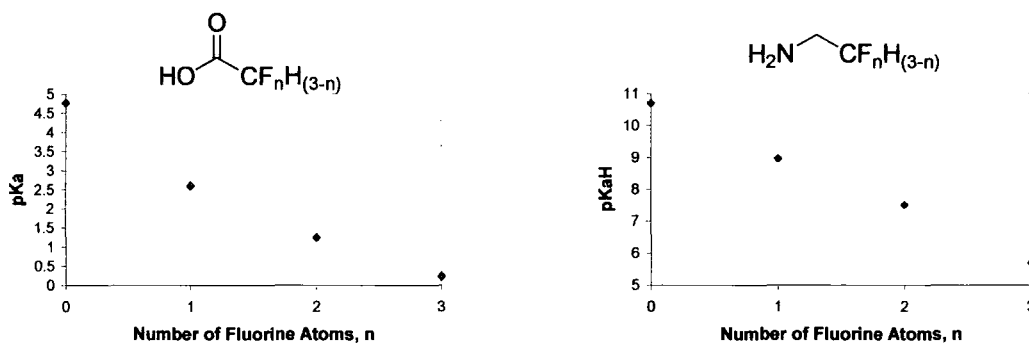


Figure 1.11

The pK_a of a potential drug target can have a significant influence on its pharmacokinetic properties, such as bioavailability¹³⁴. Relatively low basicity is often required to ensure a significant proportion of a drug molecule is in an unprotonated state, and, therefore, more able to cross lipophilic cell membranes. However, an increase in basicity has often been shown to increase binding affinity of a drug to its target receptor protein. Finding an appropriate pK_a to maximise these competing effects is a delicate balancing act¹³⁶, and fluorine incorporation can be a useful tool to modulate a drug candidate's acidity.

ii) Lipophilicity

The lipophilicity of a 'drug-like' molecule must lie in a narrow range, as stated by Lipinski to be $\log P < 5$ ¹³⁷. A drug must be sufficiently lipophilic to be able to cross phospholipid bilayer cell membranes, but if lipophilicity is too great then it may become immobilised in the lipid core, or problems with poor solubility may result.

Introduction of fluorine is one approach to altering a molecule's lipophilicity. Typically, particularly in aromatic and polyfluorinated systems, fluorination results in an increase in lipophilicity because good orbital overlap between carbon and fluorine atoms results in the C-F bond being very non-polarisable¹³⁴. However, in certain systems, such as short alkyl chains, or in the vicinity of an oxygen atom, fluorination results in a decrease in lipophilicity due to an increase in polarity.

1.7.2 Effects of Fluorine on Metabolism

Many potential drug candidates encounter difficulties when tested *in vivo* due to problems with metabolic pathways rendering the drug inactive. In particular, many such compounds are susceptible to oxidative pathways, particularly those involving Cytochrome P450 monooxygenases¹³⁴.

One approach to improving this low metabolic stability is by introduction of fluorine atoms at sites particularly sensitive to oxidation. These are often *para* sites in aromatic rings, which readily undergo oxidation to phenols. For example, in the cholesterol absorption inhibitor Ezetimib (Figure 1.12), *para*-fluorination and other structural modifications reduced metabolism to such levels whereby the required dose for activity could be decreased by 55 times, whilst increasing activity 400-fold¹³⁴.

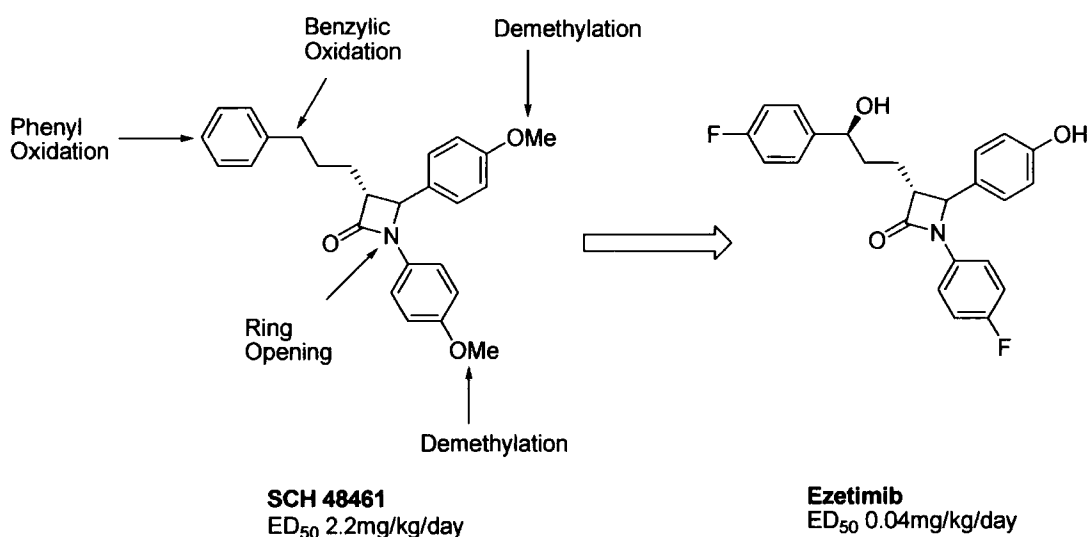


Figure 1.12

However, fluorination can in certain cases increase metabolic stability to levels where the drug persists *in vivo* and is not excreted in an acceptable timeframe. Replacement of a fluorine atom by a methyl group to give the COX-2 inhibitor Celecoxib (Figure 1.13) decreases the biological half-life from 220 hours to a more suitable 3.5 hours^{135, 138}.

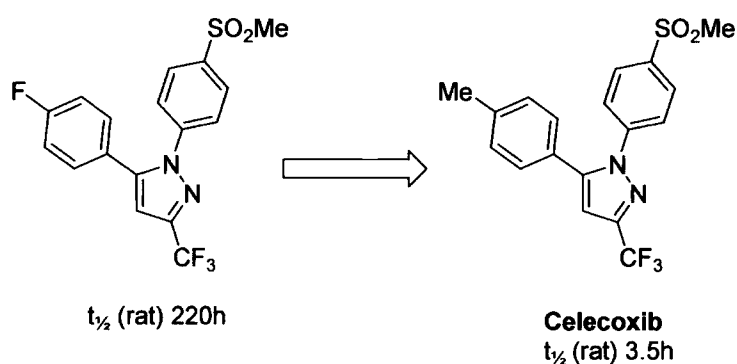


Figure 1.13

1.7.3 Effects of Fluorine on Protein Binding

Both steric and electronic factors may significantly influence the binding of a drug to its target, and introduction of fluorine may influence both of these aspects.

i) Steric Factors

In the past it has been suggested that fluorine may replace hydrogen with minimum steric perturbation, however this has been shown not to be the case. The van der Waals radius of a fluorine atom (1.47 Å) is significantly larger than hydrogen (1.20 Å), and is in fact more similar to oxygen (1.52 Å)¹³⁹. Fluorine atoms have therefore been used as bioisosteric replacements for hydroxyl groups, especially if it is necessary to remove the hydrogen bond donor character of an OH. Trifluoromethyl groups have been shown to be significantly larger in size than a methyl substituent, in fact being more similar in size, if not in shape, to an *iso*-propyl group, both having an effective Van der Waals radius of 2.20 Å¹³⁹.

These steric effects may have a significant influence on molecular conformation, which is very relevant when considering binding to proteins. For example, methoxybenzene is planar, whilst trifluoromethoxybenzene has its OCF₃ substituent orthogonal to the plane of the aromatic ring¹³⁴.

ii) Electrostatic Interactions

Electronic interactions between a C-F bond and a target receptor are moderately poorly understood, although recent work by Diederich and Müller is beginning to change this situation.

Although a C-F bond is highly polarised, it has been shown to be a poor hydrogen bond acceptor due to the tightly held nature of fluorine's lone pairs¹⁴⁰. However, other electrostatic interactions, such as dipole-dipole and charge-dipole interactions have been shown to be significant.

Crystallographic analysis of fluorinated aromatics bound to the active site of the enzyme thrombin (Figure 1.14) have shown dipole-dipole attractions between C-F bonds and C=O and C≡N groups, adopting a Burgi-Dunitz type trajectory¹⁴¹⁻¹⁴³. Attractive interactions between C-F bonds and C-H and N-H bonds have also been observed. These attractions may be utilised, for example, to stabilise the binding of an inhibitor to an active site.

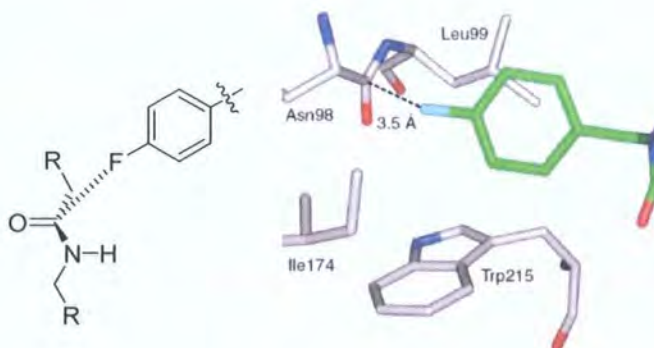


Figure 1.14

Dipolar interactions may also have a significant influence upon molecular conformation, which is significant in the binding of drug molecules into active sites of enzymes, which often have a small, complex shape. For example, a C-F bond dipole will orientate itself *anti* to an adjacent polar group, such as a carbonyl group¹⁴⁰. Vinyl fluorides have a dipole orientated in a similar direction, and a similar molecular shape to amides, as which they have been successfully employed as bioisosteric replacements (Figure 1.15).

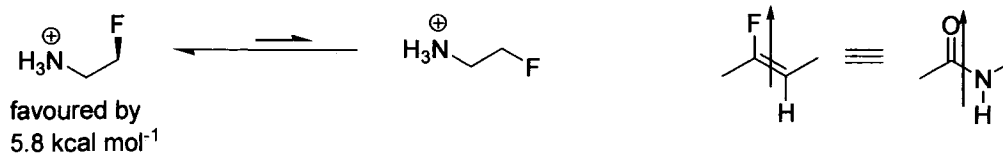


Figure 1.15

The strongest observed intermolecular attractions involving fluorine are those involving a C-F bond and an adjacent group bearing a formal positive charge. There is a strong *gauche* preference in these systems, as demonstrated in the conformation of 3F-GABA derivatives (Figure 1.16)¹⁴⁰.

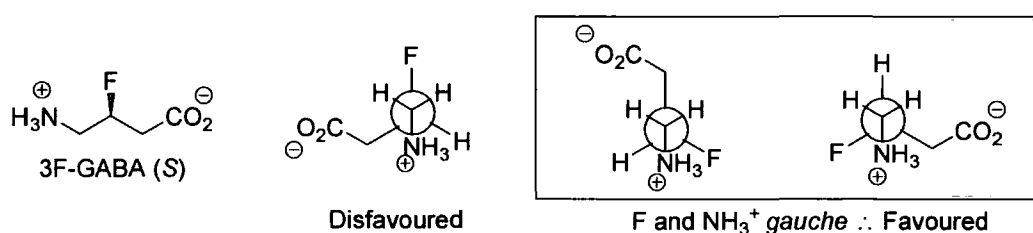


Figure 1.16

Molecular orbital interactions involving fluorine can also affect molecular conformation (Figure 1.17). For example, in alkyl systems bearing two vicinal fluorine atoms, there is a strong preference to adopt a *gauche* conformation¹⁴⁰. This is due to a hyperconjugative interaction between the C-F σ^* orbital and C-H σ orbitals on an adjacent carbon.

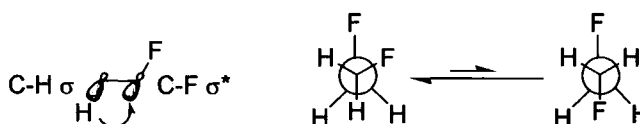


Figure 1.17

Fluorine has therefore been shown to have a significant influence on various drug properties, including physicochemical (pK_a , lipophilicity), metabolism, and steric and electrostatic factors affecting molecular conformation and binding to receptors^{144, 145}. Its incorporation into a drug candidate therefore has the potential to improve affinity, whilst

reducing side-effects, and fluorine has demonstrated to be a valuable tool for the medicinal chemist.

1.8 Conclusion

The chemistry of pyridazine derivatives is of significant current interest, particularly to pharmaceutical and materials chemists who require the efficient synthesis of a diverse range of heteroaromatic derivatives for screening programmes. The pyridazine ring system is most readily assembled by the condensation of a 1,4-dicarbonyl compound with hydrazine or by the cycloaddition of a 1,2,4,5-tetrazine derivative with a dienophile. Once formed, pyridazine derivatives, particularly halo-pyridazines, can be further functionalised by a range of nucleophilic substitution, palladium catalysed cross-coupling and metallation processes.

However, there has been little study on the reactivity of polyfluorinated pyridazine derivatives such as tetrafluoropyridazine. The preparation of fluorinated derivatives is of particular interest in medicinal chemistry for the potential improved properties fluorine can impart on drug molecules. This thesis will focus on the synthesis of polyfunctional pyridazine derivatives by sequential nucleophilic aromatic substitution reactions and on the formation of ring fused pyridazine systems by reaction with dinucleophiles.

Chapter 2

Syntheses of Polyfunctional Pyridazin-3(2H)-one Systems from Tetrafluoropyridazine

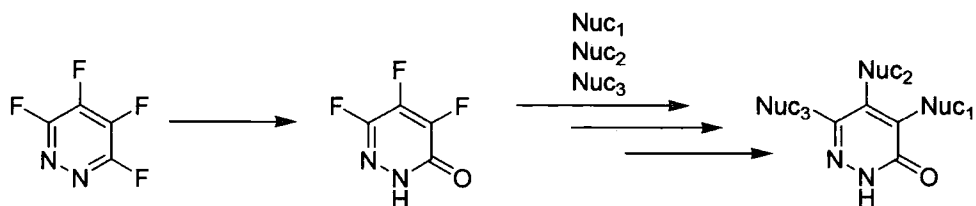
2.1 Aims and Approach

This thesis aims to describe the synthesis of a range of polyfunctional heterocyclic systems from a perfluorinated heteroaromatic precursor tetrafluoropyridazine. Such pyridazine systems are desirable in a range of applications ranging from pharmaceuticals to materials, yet their syntheses can be very difficult, owing to poor reactivity and regioselectivity of parent heteroaromatic systems.

As described in Chapter 1, traditional routes to pyridazine ring systems involve either the condensation of 1,4-dicarbonyl compounds with hydrazine, or the cycloaddition of 1,2,4,5-tetrazines with alkynes and whilst these can be effective and high-yielding approaches towards pyridazine derivatives, they may be limited in their potential to yield structurally diverse systems in large numbers using parallel synthesis approaches that are widely utilised in the pharmaceutical industry. There is still a need for efficient, high yielding syntheses of pyridazine derivatives that allow for the introduction of a high degree of diversity.

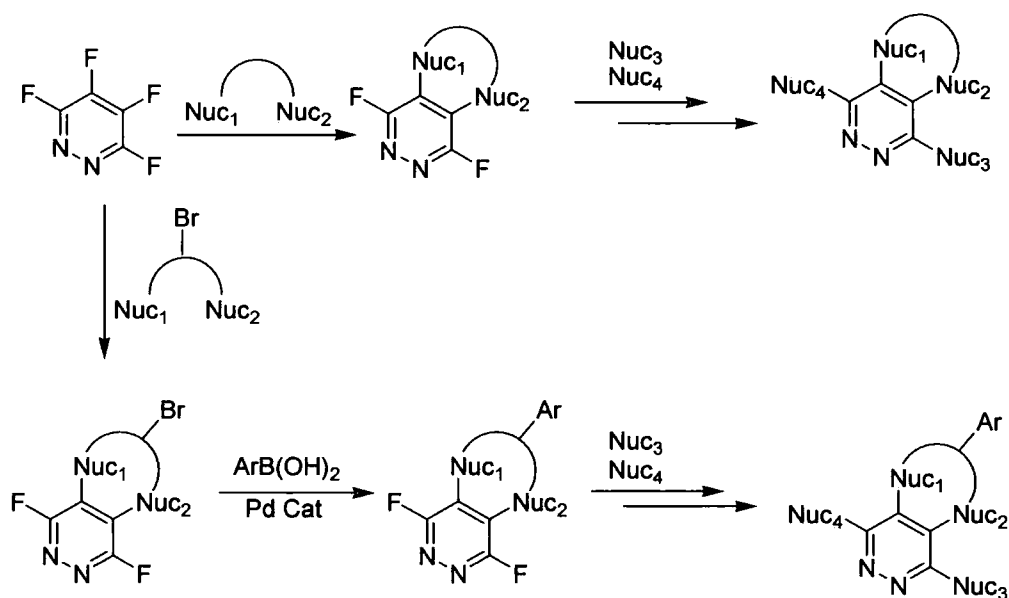
The approach of the Durham group involves the use of perfluorinated heteroaromatic scaffolds to yield polysubstituted products. For example, such highly fluorinated systems have been demonstrated to react with a range of nucleophiles under mild conditions. Such an approach may present potential benefits in terms of improved reactivity and regioselectivity and may also be suitable for diversity-oriented synthesis.

Little work has been previously described on the chemistry of tetrafluoropyridazine, so the fundamental reactivity of the system must first be established before more complex molecules can be prepared. In particular, no substitution reactions of 4,5,6-trifluoropyridazin-3(2H)-one have been reported, so the first aspect of this work focuses on determining the factors that control regioselectivity in this system. In theory, all three fluorine atoms in 4,5,6-trifluoropyridazin-3(2H)-one may be activated towards sequential displacement by nucleophiles to yield polysubstituted systems (Scheme 2.1).



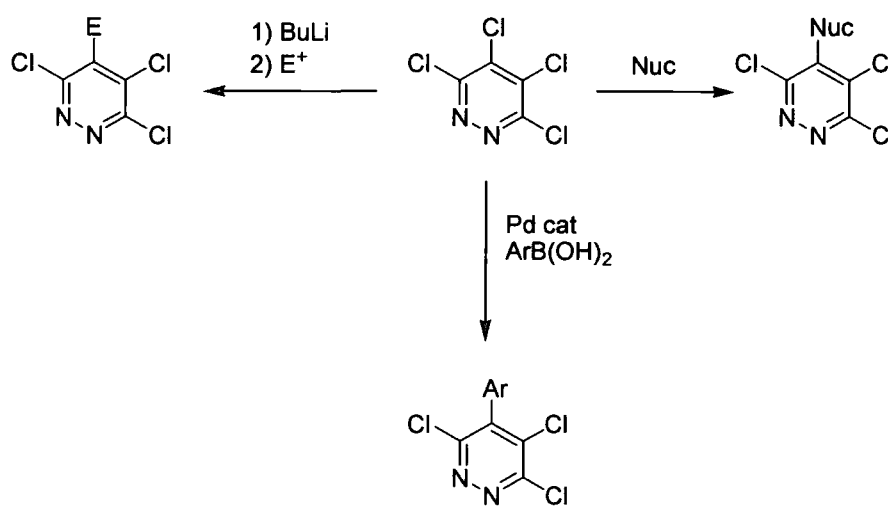
Scheme 2.1

As well as allowing for the introduction of substituent diversity, our approach also has the potential to provide some degree of scaffold diversity. The reaction of tetrafluoropyridazine with dinucleophilic species may, potentially, yield ring-fused systems, and the wide variety of dinucleophiles available should allow for the synthesis of a diverse range of fused pyridazine ring systems (Scheme 2.2). Such scaffolds will possess C-F bonds that, in theory, will be reactive towards displacement by nucleophiles thereby enabling the synthesis of libraries of compounds based on a particular scaffold. Furthermore, the use of functionalised dinucleophiles may provide an additional diversity point on the scaffold remote from the pyridazine ring. For example, brominated dinucleophiles would potentially allow palladium catalysed cross-coupling and metallation reactions to be performed.



Scheme 2.2

Finally, the chemistry of the related perhalogenated heteroaromatic tetrachloropyridazine will be explored as a potential scaffold (Scheme 2.3). Reactions of such perchlorinated heteroaromatics have been under-utilised in the past, mainly due to difficulties in product identification but now rapid X-ray crystallography techniques make the identification of products from the reactions of perchlorinated systems feasible. As well as being reactive in nucleophilic aromatic substitution processes, tetrachloropyridazine may be able to be utilised in metal-halogen exchange and palladium catalysed cross-coupling processes, allowing for a greater degree of substituent diversity.



Scheme 2.3

The following chapters describe the synthesis of a range of polyfunctional pyridazine derivatives based on the approaches described in this section.

2.2 Polysubstituted Pyridazin-3(2H)-one Derivatives

The pharmaceutical industry has a continuing requirement for the synthesis of a diverse range of polysubstituted pyridazin-3(2H)-ones bearing a varied range of ring substituents because many such compounds have been utilised as commercially available drugs and agrochemicals. Examples include the anti-platelet clotting agent Zardaverine, the anti-inflammatory Emorfazone and herbicides Pyridaben and Norflurazon, which are shown in figure 2.1 below.

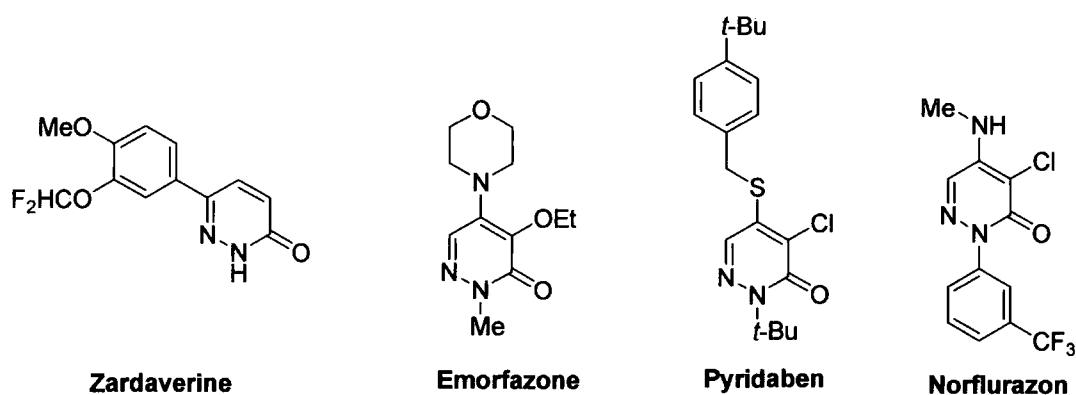
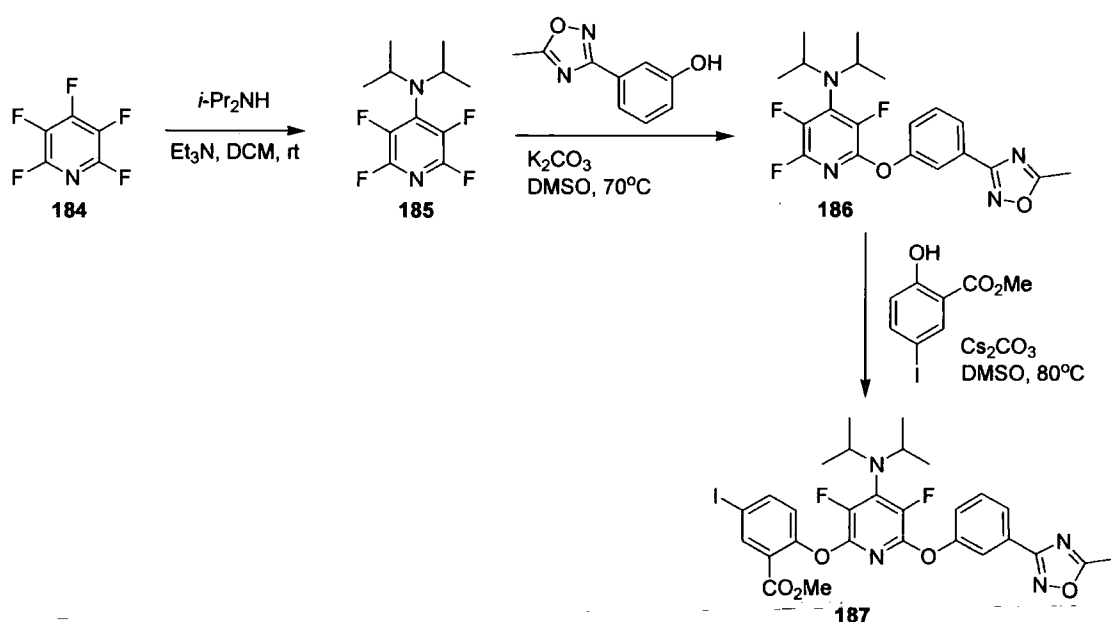


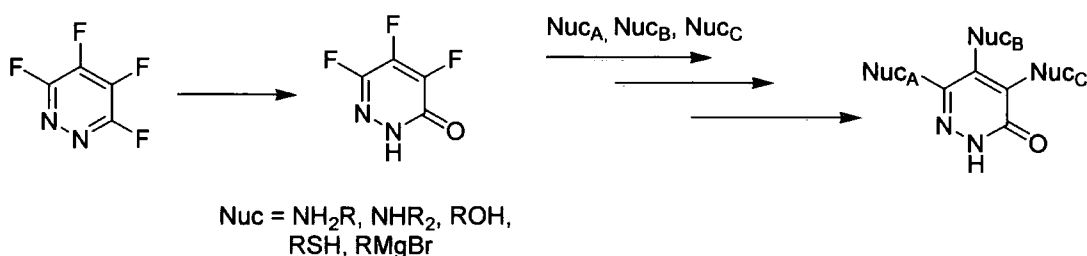
Figure 2.1

In Chapter 1 we discussed how perfluorinated heteroaromatics are highly reactive towards nucleophiles and pentafluoropyridine has been subjected to sequential nucleophilic attack to yield trisubstituted derivatives¹⁴⁶ (Scheme 2.4). Perfluorinated heteroaromatics typically demonstrate improved reactivity and regioselectivity in reactions with nucleophiles compared to chlorinated or brominated analogues and these sequential displacements on pentafluoropyridine proceed in an entirely regioselective fashion. This is ideal for the pharmaceutical industry, which requires rapid and efficient purification protocols for both the high throughput synthesis of large numbers of analogues for screening programmes and also for plant-scale synthesis of a final drug target.



Scheme 2.4

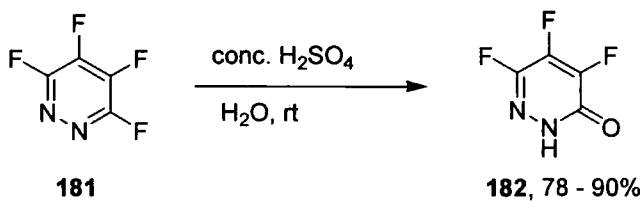
Sequential displacement of perfluorinated heteroaromatics with a range of nucleophiles should allow the production of polyfunctional systems. One such system is 4,5,6-trifluoropyridazin-3(2H)-one, whose synthesis is known from the commercially available tetrafluoropyridazine. However, to date no nucleophilic aromatic substitution reactions of 4,5,6-trifluoropyridazin-3(2H)-one have been reported in the literature, so the fundamental reactivity of this system towards nucleophiles must first be determined, examining regioselectivity as the nucleophilic species is varied. Use of a range of amines, alcohols, thiols and carbon-centred nucleophiles in first, second and third substitution processes may allow for the synthesis of an array of diversely substituted pyridazin-3(2H)-one derivatives (Scheme 2.5).



Scheme 2.5

2.3 Synthesis and Structure of 4,5,6-Trifluoropyridazin-3(2H)-one

Literature procedures were followed to accomplish the acid hydrolysis of tetrafluoropyridazine **181** to yield 4,5,6-trifluoropyridazin-3(2H)-one **182** (Scheme 2.6)¹³³. This material was sufficiently pure after extraction and washing to be used in further synthetic steps or could be recrystallised from toluene to yield analytically pure material. Yields were excellent, ranging from 78 – 90% (higher than those reported in the literature) and the hydrolysis proved to be equally efficient on reaction scales ranging from 1 – 10g.



Scheme 2.6

The product was further characterised here by X-ray crystallography, which confirmed that 4,5,6-trifluoropyridazin-3(2H)-one **182** does indeed exist as the pyridazinone tautomer, at least in the solid state (Figure 2.2). This is demonstrated by the short C=O bond length of 1.23 Å, which is more typical of a C=O double bond (~1.20 Å), rather than a C–O single bond (~1.43 Å). Intermolecular hydrogen bonding is observed in the lattice between ring NH groups and pyridazinone C=O groups.

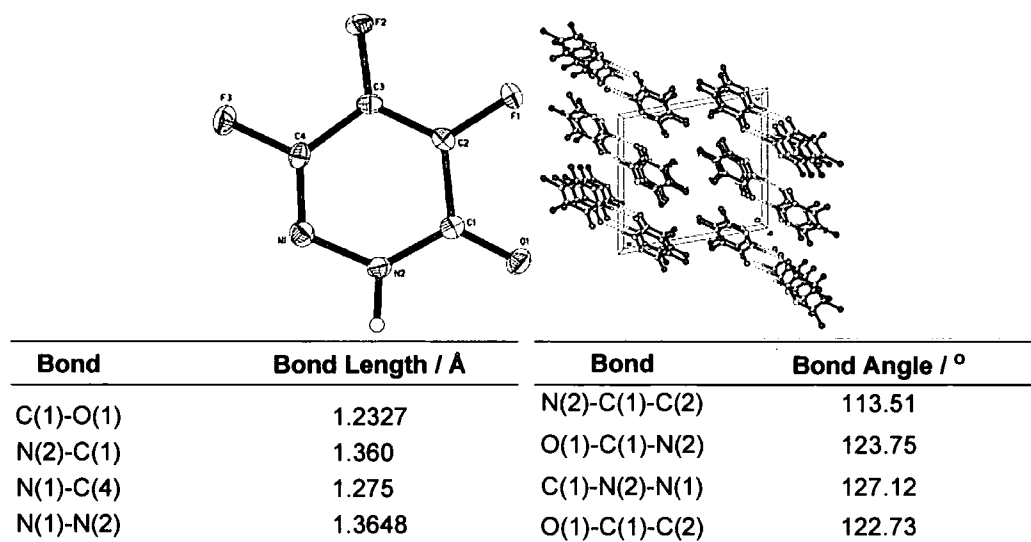


Figure 2.2: X-ray Crystal Structure of 4,5,6-Trifluoropyridazin-3(2H)-one **182**

In contrast, 2-substituted-3,5,6-trifluoro-4-hydroxypyridines, were shown by crystallography to exist as the pyridinol tautomer¹⁴⁷. This may be due to reduced electronic repulsion of the nitrogen lone pairs in the pyridazin-3(2H)-one compared to the pyridazinol, which is not a factor in the pyridine system, which suffers a loss in aromaticity on forming the pyridone tautomer (Figure 2.3).

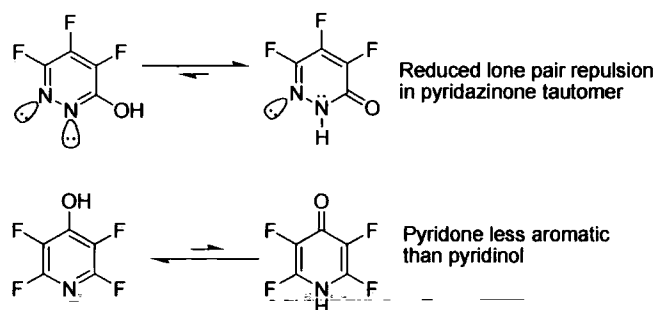


Figure 2.3

4,5,6-Trifluoropyridazin-3(2H)-one shows some evidence of tautomerisation in CDCl_3 solution, with two separate ^1H NMR resonances being visible, with the pyridazinone ring NH displaying a ^1H signal at ~ 11.4 ppm, and the hydroxyl tautomer at ~ 1.8 ppm. These tautomers are in a 2:1 ratio (NH/OH) by NMR integration. However, only one set of three resonances is displayed in the ^{19}F NMR, although signals from the two tautomers may be overlaid on top of each other.

2.4 Nucleophilic Substitution Reactions of 4,5,6-Trifluoropyridazin-3(2H)-one

To date, no examples of nucleophilic aromatic substitution reactions of 4,5,6-trifluoropyridazin-3(2H)-one have been reported in the literature. Nucleophilic substitution reactions with a range of nucleophiles of varying steric and electronic properties, including primary and secondary amines, anilines, alkoxides, thiolates and Grignard reagents, were attempted to determine the reactivity of this scaffold, in particular to examine any variation in regioselectivity depending on the nature of the nucleophile. Three possible monosubstituted isomers could be obtained by reaction of 4,5,6-trifluoropyridazin-3(2H)-one, whose fluorine atoms are all non-equivalent (Figure 2.4).

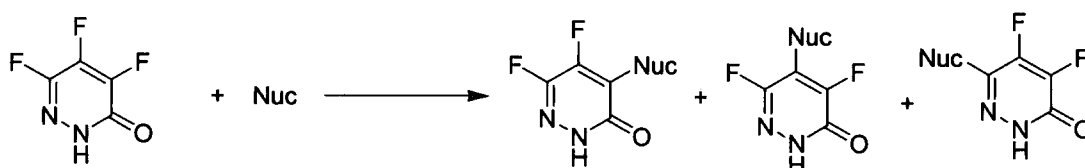


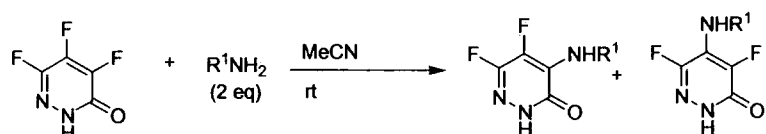
Figure 2.4

The nucleophilic aromatic substitutions were run under standard conditions to ensure that any data obtained from the isomer ratios were comparable. Each reaction was run at 25°C in acetonitrile using a standard pyridazinone concentration of $3.33\ \mu\text{mol dm}^{-3}$. Two equivalents of nucleophile were used in each case, the first to act as a nucleophile and displace fluoride, and the second to act as a base to neutralise the HF which is eliminated in this reaction. Reactions were monitored by ^{19}F NMR of the crude reaction mixture and isomer ratios of products were obtained by integration of these spectra. Reactions were allowed to proceed until ^{19}F NMR of the crude reaction mixture suggested complete conversion of starting material.

2.4.1 Nucleophilic Substitution Reactions with Amines

A range of primary, secondary and aromatic amines were chosen to provide a representative sample of nitrogen nucleophiles with different steric and electronic properties.

Reaction with primary amines proceeded efficiently at room temperature to give complete conversion to substituted products in a few hours. Primary amines were shown to give mixtures of two monosubstituted isomers (Table 2.1), where substitution at the 4-position is favoured marginally over the 5-position, with no evidence of any substitution occurring at the 6-position. The products were readily separable by column chromatography, which was pleasing as regioisomers can often be very difficult to separate.



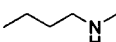
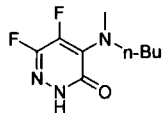
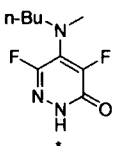

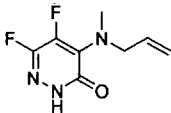
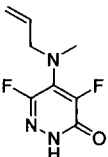

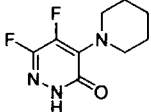


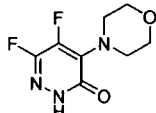


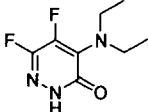

Nucleophile	Yield 4- Isomer ^a	Yield 5- Isomer ^a	Ratio 4:5- Isomers ^b
	188a, 40%	188b, 13%	60 : 40
	189a, 41%	189b, 31%	57 : 43
	190a, 49%	190b, 29%	61 : 39

^a Isolated Yield

^b Ratios determined by ¹⁹F-NMR of crude reaction mixture

Table 2.1

In the case of secondary amine nucleophiles (Table 2.2), again mixtures of 4- and 5- monosubstituted products were obtained, with the 4-substituted regioisomer being favoured in a ratio of ~ 3:1. The major isomer could be isolated by either recrystallisation or chromatography.

$\text{2,4,6-trifluoropyridazin-3(2H)-one} + \text{R}^1\text{R}^2\text{NH} \xrightarrow[\text{rt}]{\text{MeCN}} \text{4-substituted isomer} + \text{5-substituted isomer}$			
Nucleophile	Yield 4- Isomer ^a	Yield 5- Isomer ^a	Ratio 4:5- Isomers ^b
	 191a , 46%	 •	73 : 27
	 192a , 49%	 192b , 16%	73 : 27
	 193a , 52%	 •	79 : 21
	 194a , 59%	 194b , 12%	77 : 23
	 195a , 46%	 195b , 9%	77 : 23

* Not Isolated ^a Isolated Yield ^b Ratio from integration of ¹⁹F NMR of crude reaction mixture

Table 2.2

The use of substituted anilines led to a significant increase in regioselectivity (Table 2.3), with the ratio of 4- and 5-monosubstituted isomers now being greater than 9:1. Isolated yields were generally obtained by recrystallisation, and were not optimised. Impressively, for relatively unreactive nucleophiles such as anilines, reaction proceeded efficiently at room temperature in under 24 hours. Both electron-withdrawing and electron-donating substituents present on the phenyl ring were tolerated, and did not have a significant effect on either regioselectivity or reaction yield.

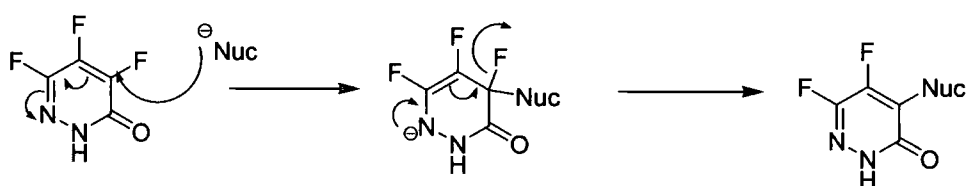
Nucleophile	Yield 4- Isomer ^a	Yield 5- Isomer ^a	Ratio 4 : 5- Isomers ^b
	 196a , 61%	 *	90 : 10
	 197a , 56%	 *	90 : 10
	 198a , 42%	 *	96 : 4
	 199a , 52%	 *	91 : 9

* Not Isolated - ^a Isolated Yield - ^b Ratio from integration of ¹⁹F NMR of crude reaction mixture

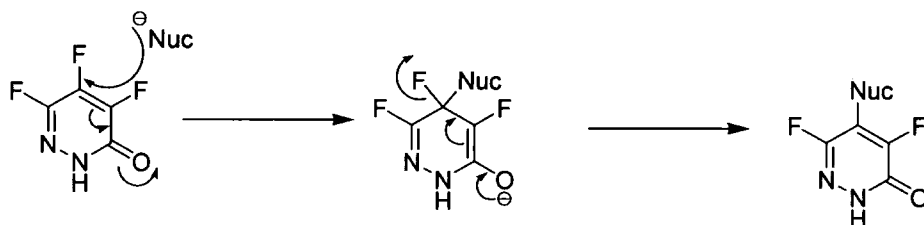
Table 2.3

In all cases, reactions of tetrafluoropyridazine with amine nucleophiles proceed at the 4- and 5-positions, with no reaction observed at the 6-position. These sites are *para* to activating ring nitrogen and allow stabilisation of the negative charge generated in the Meisenheimer intermediate onto an electronegative group (Scheme 2.7). In the case of C4 this is the pyridine-type ring nitrogen, whilst attack at C5 allows delocalisation onto the carbonyl group. Attack at C4 and C5 maximises the number of activating *ortho*-fluorine and oxygen substituents.

C4 attack



C5 attack



Scheme 2.7

It appears that as the 'soft' character of the attacking nucleophiles is increased (anilines > secondary amines > primary amines)¹⁴⁸, the regioselectivity of the reaction increases. It is not immediately obvious as to why the 4-position should react preferentially with soft nucleophiles, this must be a relatively subtle influence as a small change in nucleophile character gives a relatively large change in nucleophilic attack selectivity. The 4-position, between a C-F and C=O bond may be marginally softer than the 5-position, between two highly electron withdrawing C-F bonds (Figure 2.5).

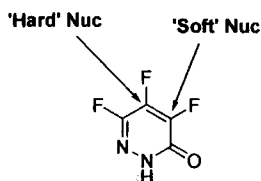


Figure 2.5

Product identification is most simply carried out by analysis of C-F coupling constants in a ^{13}C NMR spectrum. Carbon atoms bonded to fluorine are readily identifiable by their extremely large $^1J_{\text{CF}}$ coupling constant of $\sim 230\text{Hz}$. In these difluorinated pyridazin-3(2H)-one systems C-F carbon atoms are displayed as doublets of doublets, with the size of the secondary coupling constant being indicative of which isomer has been obtained. In a 4-substituted isomer ^{13}C NMR C-F signals also display a moderate secondary coupling ($^2J_{\text{CF}} \sim 17 - 33\text{Hz}$). However, in the case of 5-monosubstituted systems, the secondary coupling constants are much smaller ($^3J_{\text{CF}} \sim 8 - 13\text{Hz}$), as the carbon and fluorine atoms are further separated.

It was thought that a similar analysis of ^{19}F NMR coupling constants could allow for product identification (Table 2.4), but these are notoriously unreliable. However, in this case 4-substituted isomers consistently showed a greater $^3J_{\text{FF}}$ coupling constant of approximately $26 - 30\text{Hz}$, whilst 5-substituted isomers gave a smaller $^4J_{\text{FF}}$ coupling constant of $20 - 25\text{Hz}$. Although these ranges are close together, and an absolute value of the J_{FF} coupling constant may be fairly ambiguous, if coupling constants for both isomers can be obtained, the larger J_{FF} value represents the 4-substituted isomer, which has *ortho* fluorine atoms.

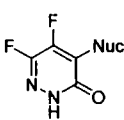
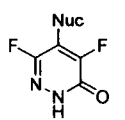




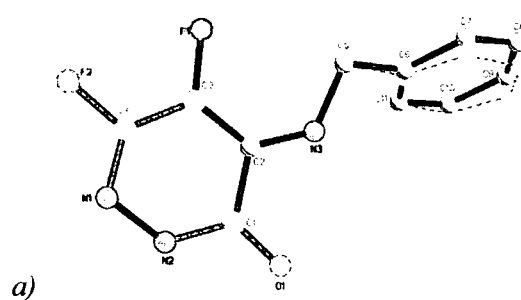
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Substituent	$^3J_{\text{FF}}$ 4- isomer / Hz	$^4J_{\text{FF}}$ 5- isomer / Hz
	26.4	24.7
BuNH	27.4	23.5
	27.5	22.9
	26.7	22.4
	29.5	20.7
NEt ₂	27.0	22.4

Table 2.4

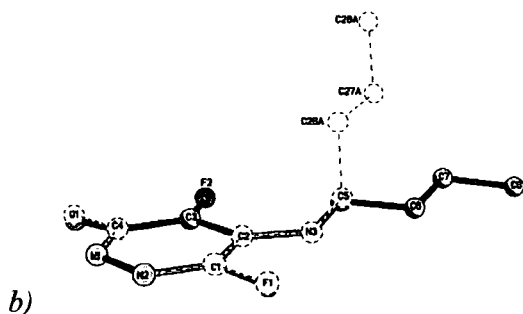
^{19}F NMR chemical shifts are not informative in this case as both 4- and 5-substituted isomers possess one fluorine atom *ortho* to ring nitrogen and one fluorine atom

para to ring nitrogen. Fluorine atoms *ortho* to ring nitrogen show a characteristic ^{19}F NMR chemical shift of ~ -100 ppm, whilst fluorine atoms not *ortho* to ring nitrogen have a ^{19}F NMR chemical shift of ~ -140 ppm.

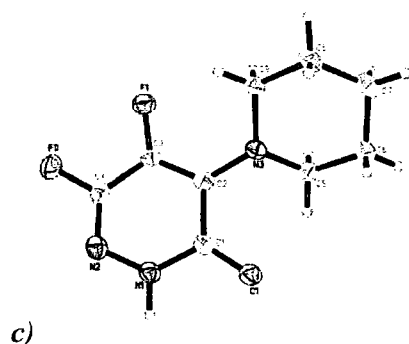
Finally, product identification for three of these derivatives, namely the 4-benzylamino **190a**, 5-butylamino **189b** and 4-piperidino **193a** derivatives (Figure 2.6), was unambiguously confirmed by X-ray crystallography and structures agreed with product assignment obtained from NMR data. The crystal structure in the two primary amino cases showed there to be two separate orientations of the alkyl chain in the unit cell.



Bond	Bond Length / Å
C(1)-O(1)	1.252
N(2)-C(1)	1.355
N(1)-C(4)	1.291
N(1)-N(2)	1.365



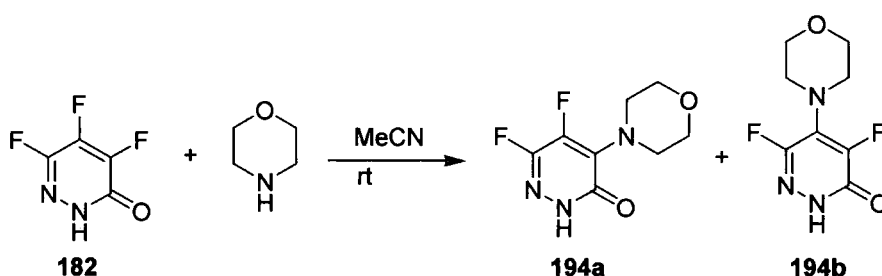
Bond	Bond Length / Å
C(4)-O(1)	1.2567
N(1)-C(4)	1.2758
N(2)-C(1)	1.355
N(1)-N(2)	1.3539



Bond	Bond Length / Å
C(1)-O(1)	1.244
N(2)-C(4)	1.285
N(1)-C(1)	1.362
N(1)-N(2)	1.362

Figure 2.6: Crystal structures of a) 4-(benzylamino)-5,6-difluoropyridazin-3(2H)-one **190a**; b) 5-(butylamino)-4,6-difluoropyridazin-3(2H)-one **189b**; c) 5,6-difluoro-4-(piperidin-1-yl)-pyridazin-3(2H)-one **193a**

The monosubstitution reactions appear to be equally efficient on a range of reaction scales, giving similar results on scales between 0.1g and 5g. The reactions did appear in certain cases to be relatively sensitive to concentration (Table 2.5), for example in the reaction of 4,5,6-trifluoropyridazin-3(2H)-one a moderate increase in selectivity in favour of the 4-isomer **194a** was observed on increasing concentration. However, using benzylamine and butylamine as nucleophile, concentration of starting material was shown to not have a significant effect. Concentrations of reagents can have a significant influence on factors such as solvation and hence affect regioselectivity.



Concentration / mol dm ⁻³	% 4- isomer	% 5- isomer
0.13	77	23
0.20	81	19
0.25	92	8

Table 2.5

The reproducibility of these results was tested by repetition of the reaction of morpholine with 4,5,6-trifluoropyridazin-3(2H)-one under standard conditions (Temperature = 25°C, Solvent = acetonitrile, Concentration = 0.20 mol dm⁻³) (Figure 2.7). These showed the ratios of isomers obtained to be consistent between runs, giving a standard deviation of 0.032 and a standard error of 0.010. This suggests that the isomer ratios can be reported to $\pm 1\%$, which is likely to be due to the error in the integration of the NMR spectrum, rather than any inconsistency of the reaction itself and the isomer ratios presented can be used with a great degree of confidence for the reaction conditions used.

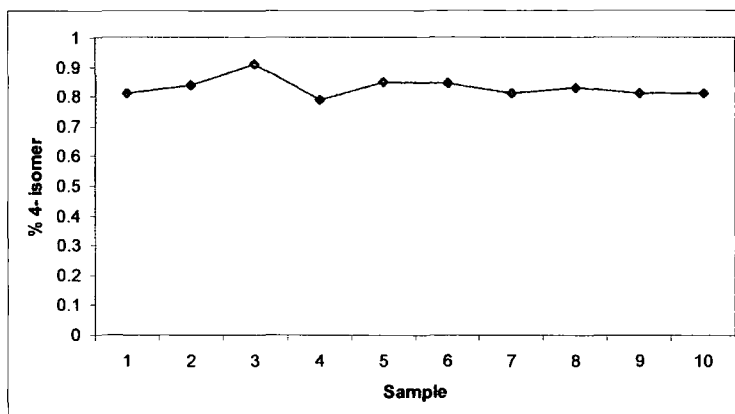
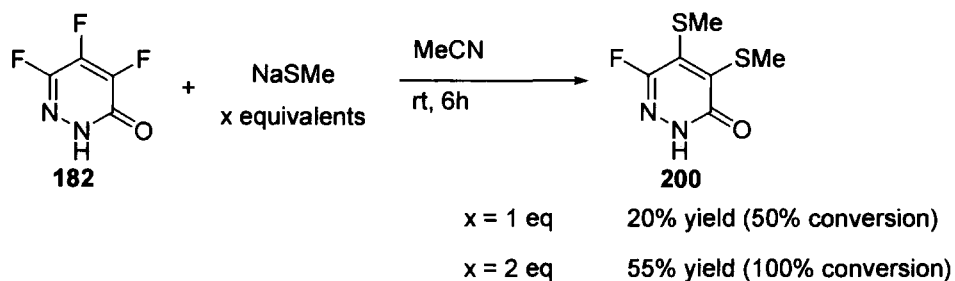


Figure 2.7

2.4.2 Nucleophilic Substitution Reaction with Thiolate Ions

With reactive nucleophiles, such as thiolate anions, it proved particularly difficult to control the nucleophilic substitution reactions of 4,5,6-trifluoropyridazin-3(2H)-one to give monosubstituted products selectively (Scheme 2.8). Reaction of a single equivalent of sodium methanethiolate with 4,5,6-trifluoropyridazin-3(2H)-one gave approximately 50% conversion to the disubstituted product **200**, suggesting that the monosubstituted product is in fact more reactive towards nucleophilic substitution than 4,5,6-trifluoropyridazin-3(2H)-one. Reaction of 4,5,6-trifluoropyridazin-3(2H)-one with two equivalents of sodium methanethiolate gave a single product **200**, disubstituted at the 4- and 5-positions and X-ray crystallography confirmed the structure of this product (Figure 2.8).



Scheme 2.8

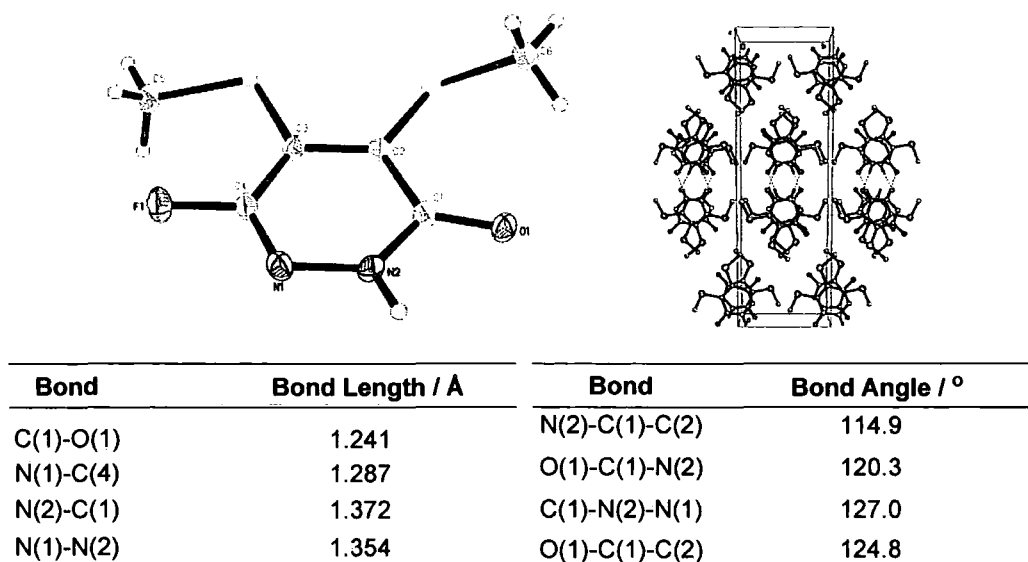


Figure 3.8: X-ray crystal structure of 6-fluoro-4,5-bis(methylthio)pyridazin-3(2H)-one **200**

Carbanions α - to sulfur are known to be stabilised¹⁴⁹ and this, therefore, activates sites *ortho* to sulfur towards nucleophilic aromatic substitution as the Meisenheimer intermediate is stabilised. It is thought that this stabilisation is a stereoelectronic effect, namely the delocalisation of the carbanion into the σ^* orbital of the adjacent C-S bond (Figure 2.9).

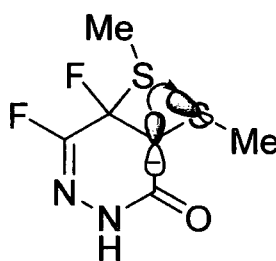


Figure 2.9

2.4.3 Nucleophilic Substitution Reactions with Basic Nucleophiles

However, when more basic nucleophiles such as alkoxides (NaOMe, NaOEt, NaOPh), Grignard reagents (PhMgBr) or bulky secondary amines (e.g. diisopropylamine, 2,2,6,6-tetramethylpiperidine) were reacted with 4,5,6-trifluoropyridazin-3(*H*)-one no substituted products could be isolated. Instead, a rapid, exothermic darkening of the

reaction mixture was observed and, on workup, a complex reaction mixture was obtained. The desired substituted product could in certain cases be observed in trace quantities (< 5%) by GC-MS, but the major components of the reaction mixture could not be identified.

It is likely that in the presence of basic nucleophiles the relatively acidic pyridazin-3(2H)-one ring NH is deprotonated and this nitrogen anion then undergoes a rapid decomposition or polymerisation process.

A potential solution to this would be to use the less reactive alcohol, rather than the sodium salt as nucleophile. Unfortunately, treatment of 4,5,6-trifluoropyridazin-3(2H)-one with methanol under reflux conditions returned only the starting material, suggesting that alcohols are not sufficiently nucleophilic to react with 4,5,6-trifluoropyridazin-3(2H)-one without deprotonation.

Therefore, the monosubstitution reactions of 4,5,6-trifluoropyridazin-3(2H)-one are mainly limited to those with amine nucleophiles, as nucleophiles of increased basicity lead to decomposition of the starting material rather than nucleophilic substitution.

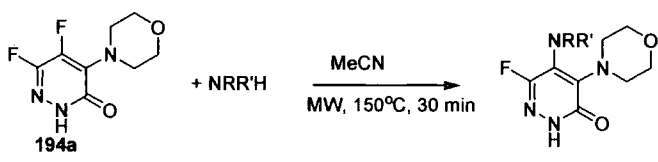
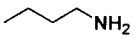
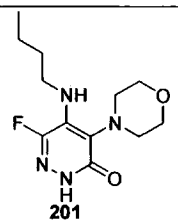
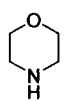
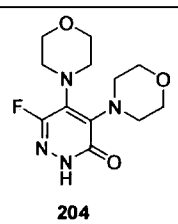
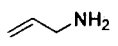

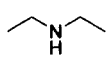
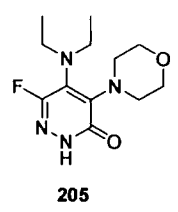
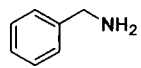
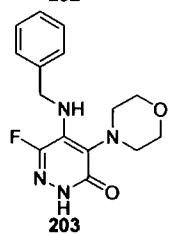
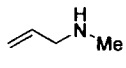
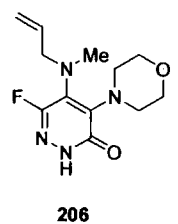
2.5 Syntheses of Disubstituted Pyridazin-3(2H)-one Derivatives

To prepare a series of disubstituted pyridazin-3(2H)-ones representative monosubstituted examples were reacted with the same range of nucleophiles to examine reactivity. Monosubstituted pyridazin-3(2H)-ones were chosen with primary amine (butylamino), secondary amine (morpholino) and aromatic amine (*p*-bromoanilino) substituents at the 4-position of the pyridazin-3(2H)-one ring as a range of first substituents with varying steric and electronic properties.

2.5.1 Reactions of 4-Morpholino-5,6-difluoropyridazin-3(2H)-one with Amine Nucleophiles

Reaction of 4-morpholino-5,6-difluoropyridazin-3(2H)-one **194a** proceeded efficiently with a range of amine nucleophiles to give the 4,5-disubstituted products in good yields (Table 2.6). The reactions did not proceed at room temperature so instead microwave irradiation was used to effect the substitution. Under these conditions the

reactions proceed, in general, to 100% conversion and give a single product. Isolated yields are obtained by a single recrystallisation from acetonitrile, and are not optimised.

					
Nucleophile	Product	Isolated Yield (%)	Nucleophile	Product	Isolated Yield (%)
	 201	55%		 204	54%
	 202	56%		 205	25%*
	 203	62%		 206	43%

* Only 70% conversion by ^{19}F NMR

Table 2.6

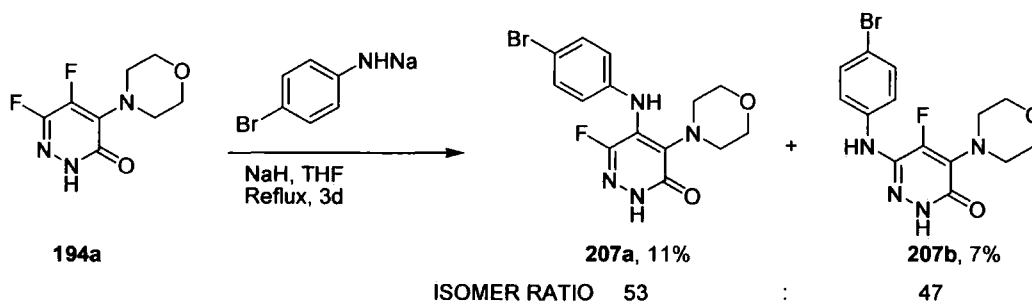
The replacement of a fluorine atom with an amine substituent ensures that this system is significantly less reactive than 4,5,6-trifluoropyridazin-3(2H)-one. No reaction was observed at room temperature, and the conversion was best effected by heating the reaction mixture to reflux for 72 hours, or using microwave irradiation at 150°C for 30 minutes. This is because the replacement of a highly electron-withdrawing fluorine atom with an amine substituent renders the heteroaromatic ring significantly less electron deficient, so much less reactive towards nucleophilic displacement.

The products were identified as the 4,5-disubstituted derivatives, rather than 4,6-disubstituted from examination of their ^{19}F NMR chemical shifts, which range from -94 –

-101ppm. These chemical shifts are characteristic of fluorine that is deshielded by an *ortho* ring nitrogen, indicating the presence of a fluorine atom at the 6-position, therefore substitution of the 5-fluorine must have occurred.

Reaction of the parent scaffold with anilines was also examined, however these were not sufficiently nucleophilic to react under standard microwave irradiation conditions. Instead, the sodium salt of 4-bromoaniline was prepared by deprotonation with sodium hydride, and this was heated to reflux with 4-morpholino-5,6-difluoropyridazin-3(2H)-one **194a** (Scheme 2.9) to yield both 4,5- (**207a**) and 4,6- (**207b**) disubstituted products in an approximately 1:1 ratio in 100% conversion. Separation of the isomers proved difficult, and was achieved by mass directed HPLC, although pure samples of each isomer could only be obtained in 11% and 7% yield.

It seems likely that use of a less reactive aniline nucleophile led to more of the thermodynamically stable 4,6-disubstituted product, which has less steric clashing between its substituents. More reactive nucleophiles give the 4,5-disubstituted compound selectively as the kinetic product, by reaction at the most electrophilic site.



Scheme 2.9

2.5.2 Reaction of 4-(4-Bromophenylamino)-5,6-difluoropyridazin-3(2H)-one with Amine Nucleophiles

Reaction also proceeded effectively with the 4-bromoanilino substituted pyridazin-3(2H)-one **198a** and a range of primary amine nucleophiles to produce the 4,5-disubstituted products **208** and **209** (identified as described previously from analysis of ^{19}F NMR chemical shifts). Isolated yields were excellent, obtained by filtration of the reaction

mixture through a short column of silica gel. The reaction with the sulfur nucleophile sodium ethanethiolate also provided the disubstituted product **212** in excellent yield.

However, the reaction of **198a** with secondary amines such as diethylamine and morpholine was extremely slow, even under forcing microwave irradiation conditions. Conversion to the desired disubstituted products **210** and **211** was around 20% by crude ^{19}F NMR, and mass directed automated purification allowed the isolation of this in around 15% yield. It is likely that the poor yields in these cases are due to steric hindrance, which indicates the difficulties in placing a bulky secondary amine *ortho* to a sterically demanding aniline substituent.

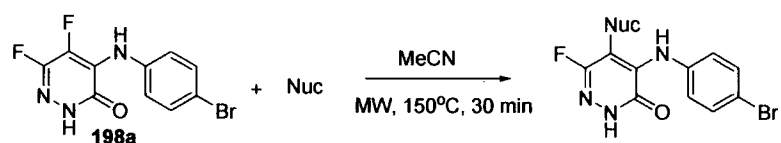
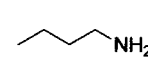
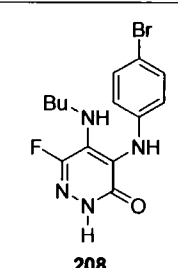
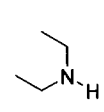
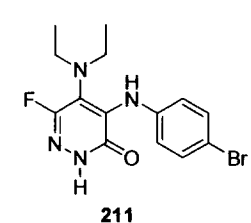
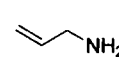
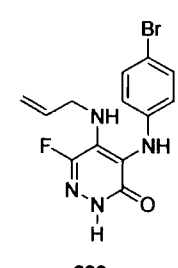
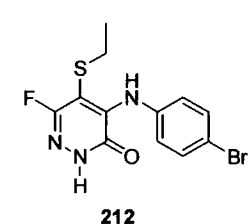
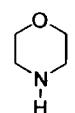
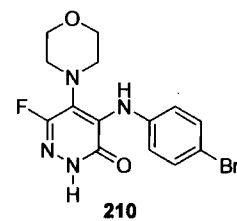
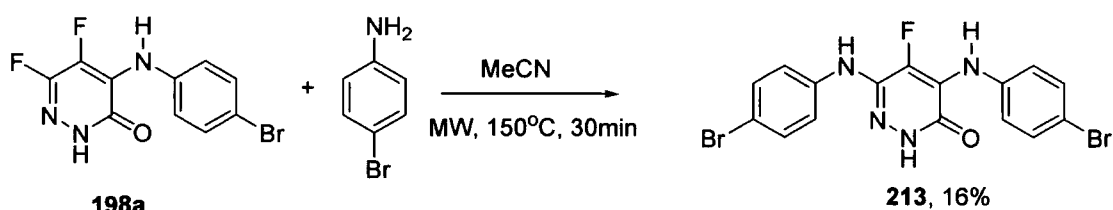
					
Nucleophile	Product	Isolated Yield (%)	Nucleophile	Product	Isolated Yield (%)
	 208	90		 211	15
	 209	45	NaSEt	 212	90
	 210	18			

Table 2.7

These steric effects were further exemplified in the reaction of **198a** with a second equivalent of 4-bromoaniline (Scheme 2.10), which again required formation of the sodium salt by deprotonation with NaH to achieve reaction. This yielded only the 4,6-disubstituted product **213** in poor yield and demonstrates the large steric clashing between two adjacent aromatic rings. The second substituent is therefore forced to the less reactive, although less sterically hindered 6-position, to give the thermodynamic product. The product in this case was identified by analysis of its ^{19}F NMR chemical shift, which at -139 ppm is characteristic of fluorine that is not *ortho* to ring nitrogen.



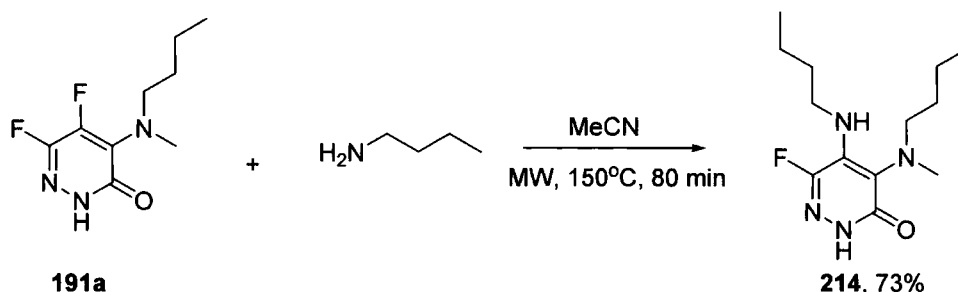
Scheme 2.10

2.5.3 Reaction of 4-Butylamino-5,6-difluoropyridazin-3(2H)-one and 4-benzylamino-5,6-difluoropyridazin-3(2H)-one with Amine Nucleophiles

Surprisingly, when the two 4-primary amino substituted pyridazin-3(2H)-ones 4-butylamino-5,6-difluoropyridazin-3(2H)-one **189a** and 4-benzylamino-5,6-difluoropyridazin-3(2H)-one **190a** were heated with an amine nucleophile under microwave irradiation at 150°C, even for extended periods of time of up to one hour, conversion to the desired disubstituted product was observed to be less than 5% by LC-MS and ^{19}F NMR of the crude reaction mixture. This was in contrast to the 4-secondary amino and 4-anilino derivatives, which generally reacted very efficiently in high yield under these conditions as described above.

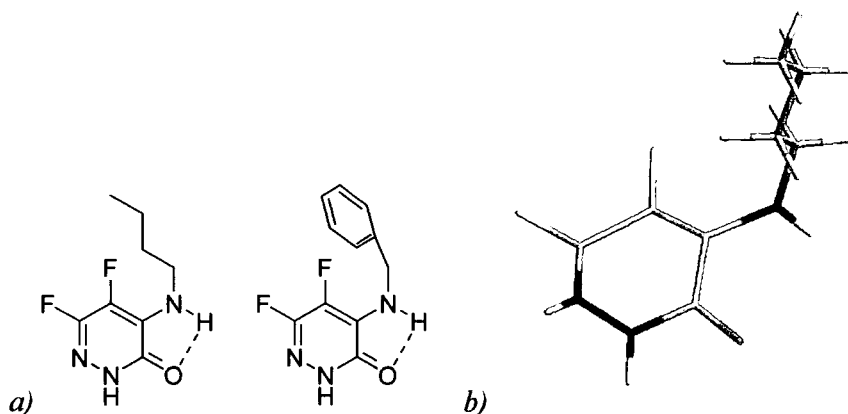
It was noted that methylation of the amine substituent NH allowed further substitution processes to proceed effectively. Thus, reaction of 4-(*N*-butyl-*N*-methylamino)-5,6-difluoropyridazin-3(2H)-one **191a** with *n*-butylamine (Scheme 2.11) yielded the disubstituted product **214** in good yield, confirming that this lack of reactivity was related to the degree of substitution on the amine substituent nitrogen, rather than any specific issues with a butyl or benzyl substituent. This suggests that secondary amine

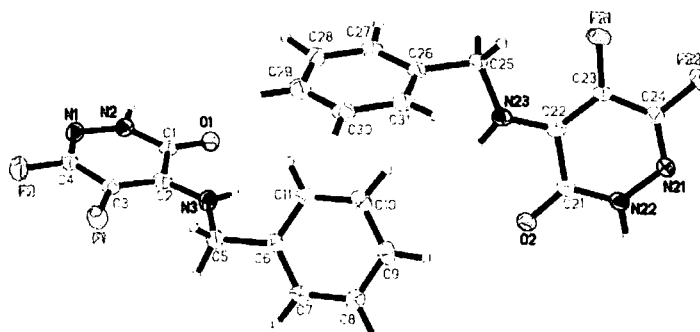
substituents at the 4-position allow further nucleophilic displacements to proceed whilst 4-primary amino pyridazin-3(2H)-ones are unreactive towards further substitution.



Scheme 2.11

The possibility of an unfavourable conformation of the pendant alkyl chain blocking further substitution was not supported by examination of the crystal structure. It was postulated that an intramolecular hydrogen bond between the primary amino NH and the adjacent pyridazin-3(2H)-one C=O may force the alkyl chain into a position that blocks the remaining fluorine atoms (Figure 2.10a). Such a hydrogen bond would, of course, not be present if the substituent was derived from a secondary amine. However, there was no evidence for the presence of such a hydrogen bond in the solid state (Figure 2.10c), and this would be even less likely under the high temperatures used experimentally. MM2 molecular mechanics simulations also suggested that in the minimum energy conformation of this molecule there was minimum steric influence by the pendant alkyl group (Figure 2.10b)

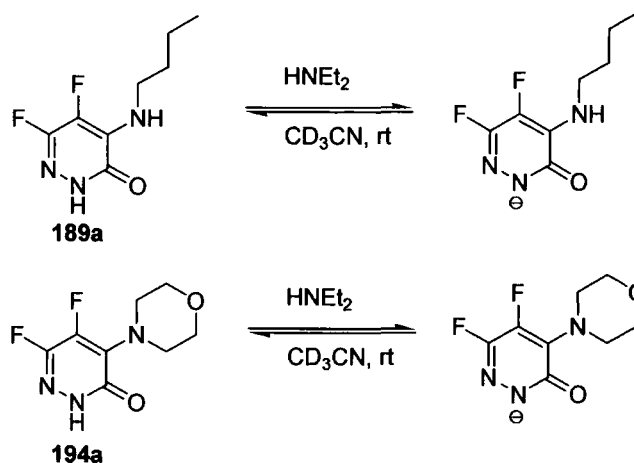




c)

Figure 2.10: a) Postulated deactivated conformation of 4-primary amino pyridazin-3(2H)-ones; b) MM2 molecular mechanics minimum energy conformation of 4-(butylamino)-5,6-difluoropyridazin-3(2H)-one **189a** c) X-ray crystal structure of 4-(benzylamino)-5,6-difluoropyridazin-3(2H)-one **190a** showing no evidence of intramolecular hydrogen bonding;

Another explanation that is unlikely is deprotonation of the NH of the amine substituent by the nucleophile. ^1H NMR of the 4-butylamino **189a**, 5-butylamino **189b** and 4-morpholino **194a** pyridazin-3(2H)-one derivatives in CD_3CN were measured before and after the addition of diethylamine as a potential base. This showed the disappearance of the ring NH signal at approximately 10 ppm due to rapid exchange in all three cases, but the amine substituent NH was unaffected, suggesting that it was not sufficiently acidic to be deprotonated to any significant extent under these conditions (Scheme 2.12). It is unlikely that the pK_a of an amine substituent will be such to allow deprotonation by another amine.



Scheme 2.12

A simple consideration of the inductive electron donating character of these groups cannot explain this observation, as a secondary amine substituent could be expected to be a more powerful electron donor than a primary amine, due to its two electron donating alkyl groups.

An analysis of the ^{13}C NMR chemical shifts of various 4-substituted-5,6-difluoropyridazin-3(2H)-ones (Table 2.8) suggests that the primary amino substituted derivatives are in fact the most electron rich. The C5 carbon, which is the site most reactive towards nucleophilic displacement, of 4-secondary amino and 4-bromoanilino derivatives are up to 6 ppm deshielded relative to 4-primary amino derivatives.

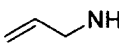
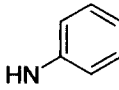
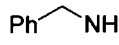
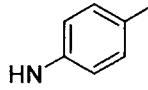
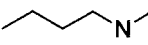
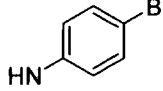
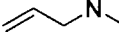
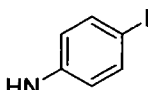
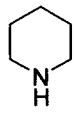
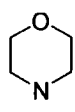
Substituent	^{13}C δ 5- position / ppm	Substituent	^{13}C δ 5- position / ppm
	131.2	NEt_2	136.5
BuNH	130.8		132.2
	131.7		131.9
	136.5		136.2
	135.0		132.6
	137.4		
	137.0		

Table 2.8

The observation that the 4-primary amino pyridazin-3(2H)-ones are more electron rich than 4-secondary amino pyridazin-3(2H)-ones is likely to be a stereoelectronic effect. A small primary amine substituent with a single alkyl chain can easily be oriented in the same plane as the pyridazin-3(2H)-one ring, whilst steric repulsion between the two alkyl substituents of a secondary amine and the adjacent C-F and C=O bonds is likely to force the amine substituent to be twisted out of the plane of the pyridazin-3(2H)-one ring. This will lead to better orbital overlap in the case of the in-plane primary amine substituent, so in

fact these less sterically bulky substituents act as more effective electron donating groups, and render the pyridazin-3(2H)-one ring less electron deficient, so less reactive towards nucleophilic substitution.

This twisting of the alkyl substituent was observed in the crystal structure of 5,6-difluoro-4-(piperidin-1-yl)pyridazin-3(2H)-one, shown by the torsion angle between C1 and C5 on the diagram, which is 50° , and C3 and C9, which is 15° . If the two rings were in the same plane, these two torsion angles would be expected to have the same value. This twisting, therefore, means there is less effective orbital overlap in this secondary amine substituted system, so it is a worse electron donor, and therefore less deactivating towards further nucleophilic substitution.

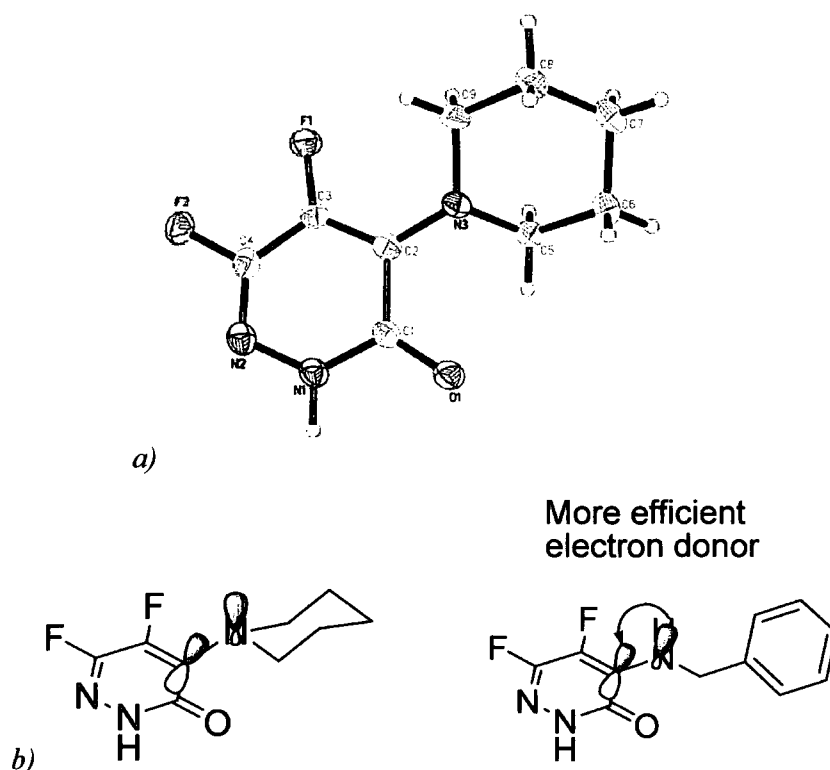


Figure 2.11: a) X-ray crystal structure of 5,6-difluoro-4-(piperidin-1-yl)-pyridazin-3(2H)-one **193a**; b) Postulated conformations and orbital interactions in 4-primary amino and 4-secondary amino pyridazin-3(2H)-ones

A similar stereoelectronic effect is observed in the basicity of dimethylaniline derivatives¹⁵⁰. *o*-Dimethylaminotoluene **216** is a stronger base than dimethylaniline **215** by almost 1-pK-unit, much more than could be expected by the inductive electron donation of

the *ortho* methyl substituent (Figure 2.12). This observation has been explained by a steric interaction between the methyl and amine substituents impeding resonance delocalisation of the nitrogen lone pair into the aromatic ring and therefore increasing the basicity of *o*-dimethylaminotoluene **216**.

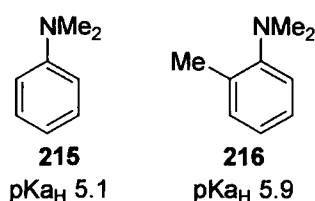
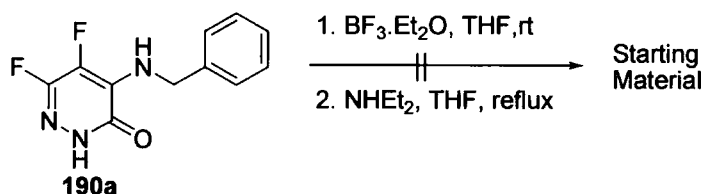


Figure 2.12

It was thought that Lewis acid activation may reduce electron density on the ring, and thus allow the second substitution process to proceed. However, on addition of $BF_3 \cdot Et_2O$ to 4-benzylamino-5,6-difluoropyridazin-3(2H)-one **190a**, followed by reaction with diethylamine at reflux, only the starting material was obtained (Scheme 2.13).



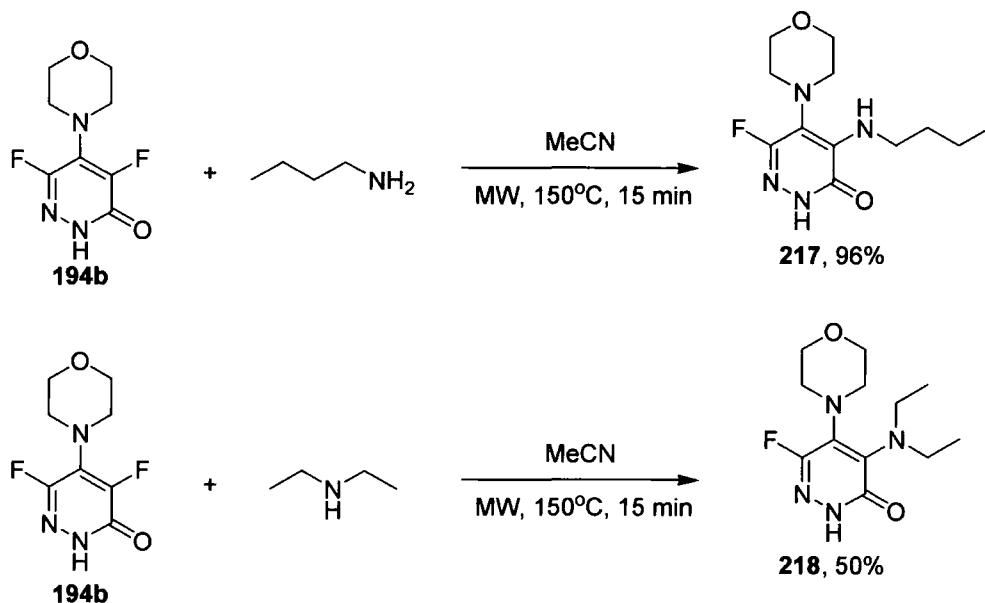
Scheme 2.13

2.5.4 Substitutions on 5-Substituted-4,6-Difluoropyridazin-3(2H)-ones

Although the major products of monosubstitution with amine nucleophiles in all cases were substituted at the 4-position, several of the corresponding 5-monosubstituted isomers could be successfully isolated. Reactions of 4,6-difluoro-5-morpholinopyridazin-3(2H)-one and 5-(butylamino)-4,6-difluoropyridazin-3(2H)-one with nucleophiles have been examined.

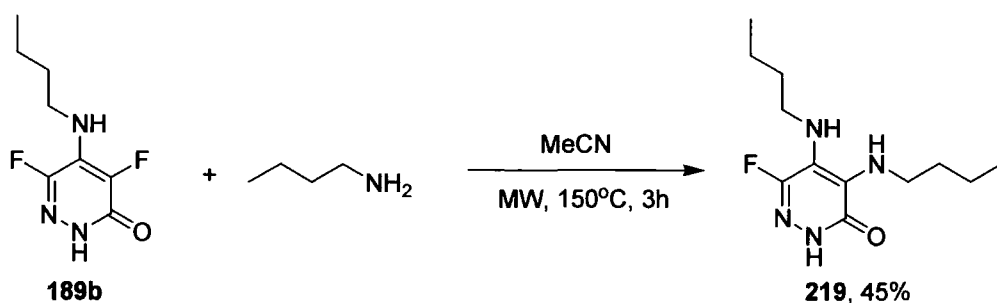
4,6-Difluoro-5-morpholinopyridazin-3(2H)-one **194b** reacted with amine nucleophiles in moderate to good yield at the most activated 4-position to give the 4,5-disubstituted derivatives **217** and **218** (Scheme 2.14). The isolated yield was reduced when

diethylamine was used as nucleophile compared to *n*-butylamine, due to steric hindrance of attack of a bulky secondary amine nucleophile *ortho* to a bulky ring substituent.



Scheme 2.14

In contrast to the 4-primary amino pyridazin-3(2H)-ones which were completely unreactive towards further nucleophilic displacements, 5-(butylamino)-4,6-difluoropyridazin-3(2H)-one **189b** reacted, albeit very slowly upon prolonged heating, with a second equivalent of *n*-butylamine to give the 4,5-disubstituted product **219** (Scheme 2.15). Extended microwave irradiation at 150°C for 3 hours gave 65% conversion to the disubstituted product by ¹⁹F NMR, which could be isolated by mass directed automated purification in moderate yield.

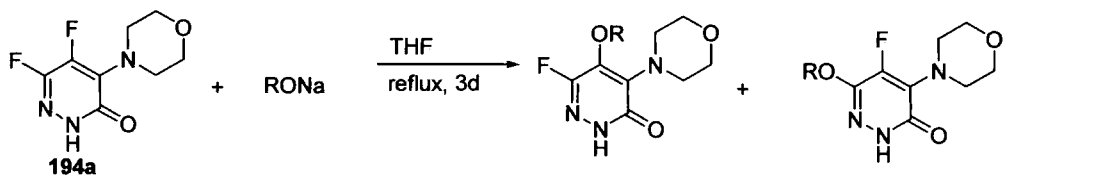
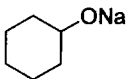
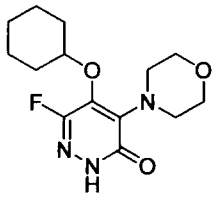
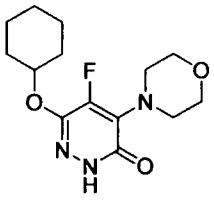

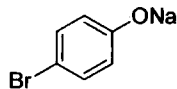
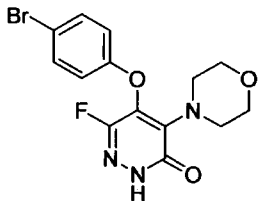


Scheme 2.15

2.5.5 Reaction of Monosubstituted Pyridazin-3(2H)-ones with Oxygen Nucleophiles

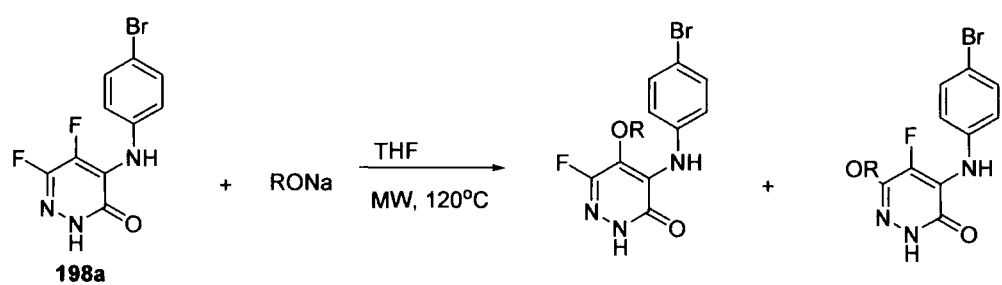
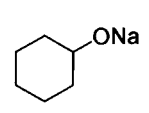
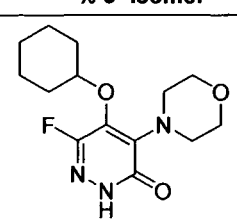
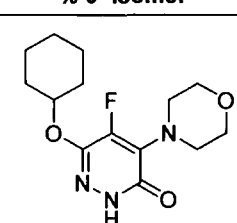
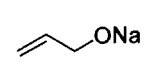
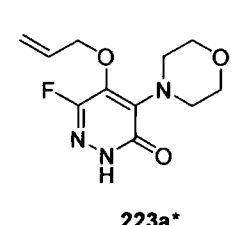
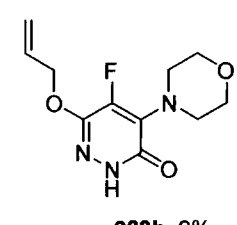
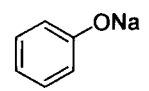
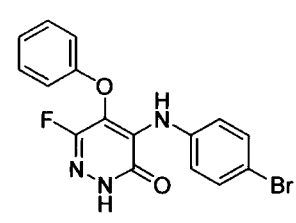
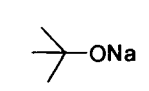
Both 4-morpholino-5,6-difluoropyridazin-3(2H)-one **194a** (Table 2.9) and 4-(4-bromophenyl-amino)-5,6-difluoropyridazin-3(2H)-one **198a** (Table 2.10) were reacted with a range of sodium alkoxide and phenoxide salts using THF as solvent.

Although the decomposition that occurred on reaction of 4,5,6-trifluoropyridazin-3(2H)-one was not observed, conversions to disubstituted products were still extremely low, even after extended reflux or microwave irradiation periods and, in several cases, mixtures of 4,5- and 4,6-disubstituted products were obtained. Product isolation was difficult in all cases, due to the low conversions and difficult separation of regioisomers, and was accomplished in low isolated yield by mass directed HPLC.

				
Nucleophile	Conversion (%)	Yield 5- isomer	Yield 6- isomer	Ratio 5:6- Isomers ^a
	50	 220a , 19%	 220b , 12%	68 : 32
	0			
	48	 221a , 23%		100 : 0

^a Isomer ratios determined by integration of crude ¹⁹F NMR spectra

Table 2.9

				
198a				
Nucleophile	Conversion (%)	% 5- isomer	% 6- isomer	Ratio 5:6- Isomers ^a
	7	 222a*	 222b*	40 : 60
	21	 223a*	 223b, 9%	19 : 81
	12	 224a, 7%		100 : 0
	0			

^a Isomer ratios determined by integration of crude ¹⁹F NMR spectra

* Not isolated

Table 2.10

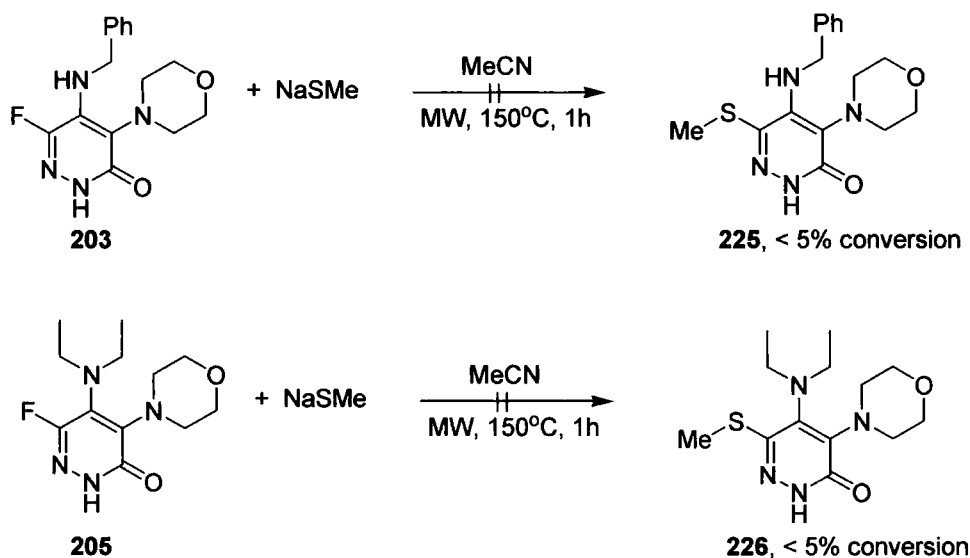
It is likely that this lack of reactivity is due to the presence of the acidic pyridazin-3(2H)-one ring NH which may interact with relatively basic alkoxide nucleophiles, which deactivates the system towards nucleophilic aromatic substitution. With extremely hindered, and highly basic nucleophiles such as sodium *tert*-butoxide, no conversion is

observed. This is likely to be due to the bulky *tert*-butoxide acting exclusively as a base, rather than a nucleophile, as proton abstraction is a less sterically demanding process.

Ring deprotonation may lead to the observed decrease in regioselectivity compared to the amine nucleophiles, as nucleophilic substitution on a deactivated negatively charged system is more likely to give the thermodynamic 4,6-disubstituted product.

2.6 Displacement of Fluorine from 6-Fluoro-4,5-diamino Pyridazin-3(2H)-one Systems

The displacement of the final ring fluorine from 5-(benzylamino)-6-fluoro-4-morpholinopyridazin-3(2H)-one **203** and 5-(diethylamino)-6-fluoro-4-morpholinopyridazin-3(2H)-one **205** was attempted using amine or alkoxide nucleophiles under forcing microwave irradiation conditions, however it did not proceed to any appreciable extent (Scheme 2.16). With highly reactive nucleophiles such as thiolate anions, the desired trisubstituted product could be observed by LC-MS in trace quantities (< 5%), but was not isolable. The fluorine atom at the 6-position of 4,5-disubstituted pyridazin-3(2H)-ones is therefore resistant to nucleophilic attack under the conditions investigated.



Scheme 2.16

2.7 Conclusions

4,5,6-Trifluoropyridazin-3(2H)-one has proven to be an excellent scaffold for the synthesis of nitrogen functionalised pyridazin-3(2H)-ones. An array of 4,5-disubstituted 6-fluoro pyridazin-3(2H)-ones have been synthesised starting from tetrafluoropyridazine. Acid hydrolysis of tetrafluoropyridazine affords 4,5,6-trifluoropyridazin-3(2H)-one in excellent yield, which has then been reacted with a range of nucleophilic species to examine its reactivity towards nucleophiles. A selection of some of the systems synthesised are shown in figure 2.13.

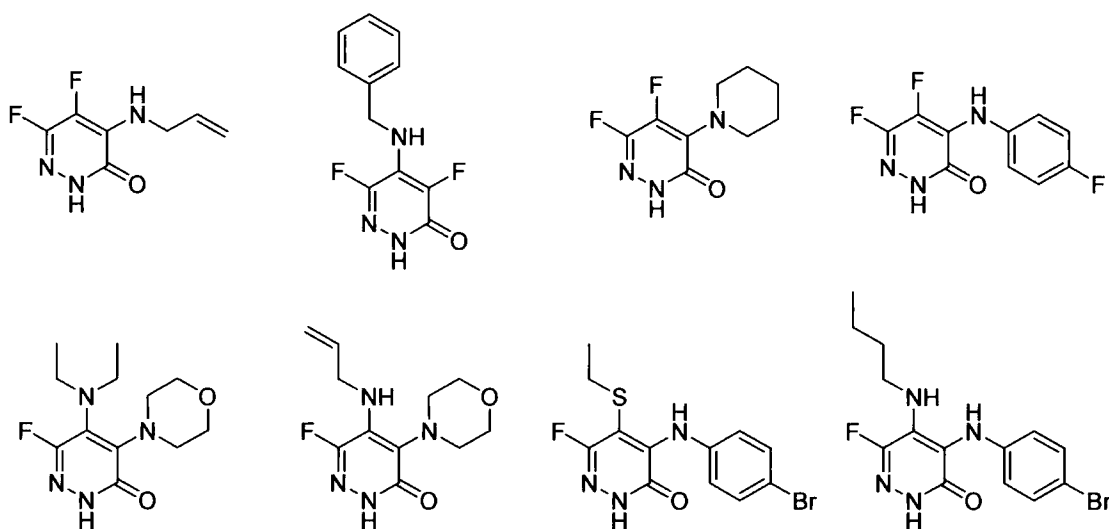


Figure 2.13

Monosubstitution reactions of 4,5,6-trifluoropyridazin-3(2H)-one with a broad selection of nitrogen nucleophiles proceed to give a mixture of 4- and 5-substituted regioisomers, which are readily separable. The regioselectivity of such monosubstitution reactions increases as the soft electronic character of the nucleophile increases, being highest for anilines (up to 96 : 4 in favour of 4-isomer).

The second substitution proceeds regioselectively at the 5-position for the 4-morpholino and 4-bromoanilino pyridazin-3(2H)-one systems in reactions with a range of amines. With bulky nucleophiles such as secondary amines or anilines, yields can be reduced, and in some cases some 4,6-disubstituted product may result from substitution of the less sterically hindered 6-position.

However, difluoro-pyridazin-3(2H)-ones functionalised with a primary amine substituent at the 4-position are unreactive towards a second substitution step. This effect is thought to be stereoelectronic in origin, resulting from effective donation from the amine lone pair into the aromatic system.

Also, both 4,5,6-trifluoropyridazin-3(2H)-one and monosubstituted systems fail to give substitution products in high yield in reaction with basic nucleophiles, such as alkoxides. This is likely to be due to deprotonation of the acidic pyridazin-3(2H)-one ring NH, which either deactivates the system towards further substitution, or in the case of 4,5,6-trifluoropyridazin-3(2H)-one leads to decomposition.

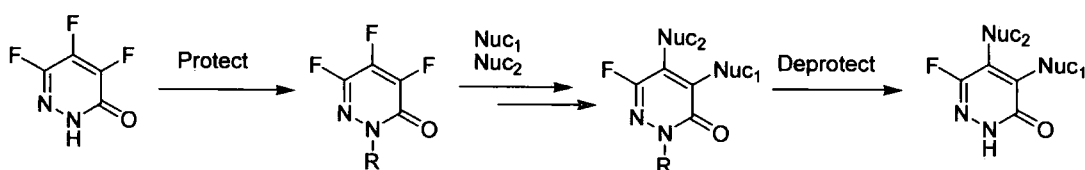
Chapter 3

Chemistry of *N*-Functionalised Polyfluoropyridazin-3(2*H*)-one Derivatives

3.1 Introduction

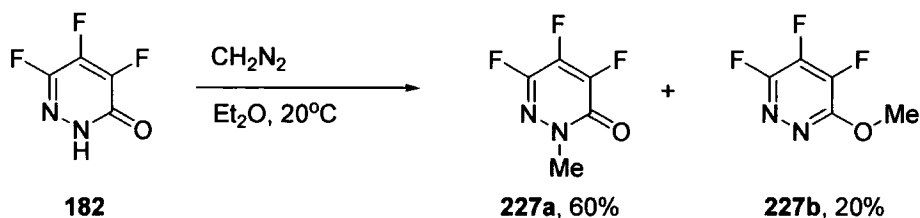
Although 4,5,6-trifluoropyridazin-3(2*H*)-one proved to be an excellent scaffold for regioselective functionalisation in reactions involving amines, reactions with nucleophiles such as alkoxides and Grignard reagents were limited by the basicity of the nucleophile. It is thought that interaction of the base with the relatively acidic pyridazin-3(2*H*)-one ring NH leads to deactivation of the system towards substitution, or to decomposition or polymerisation of the starting material.

We expect that alkylation of the ring NH to prevent competing deprotonation will allow the potential range of nucleophiles compatible with this system to be expanded. A suitable protecting group should be identified that can be easily introduced, is stable to the reaction conditions and can be readily removed when no longer required (Scheme 3.1). A similar range of nucleophilic substitutions will be performed on the protected derivatives as described in Chapter 2, however the reactions of alkoxide nucleophiles in particular will be examined to determine the feasibility of efficiently introducing oxygen substituents onto the ring.



Scheme 3.1

The only report of *N*-alkylation of 4,5,6-trifluoropyridazin-3(2*H*)-one **182** was described by Chambers *et al.* in 1968, utilising diazomethane as the alkylating agent (Scheme 3.2). This produced the corresponding *N*-methylated compound **227a** in good yield, along with the *O*-methylated compound **227b** in a 3 : 1 ratio.

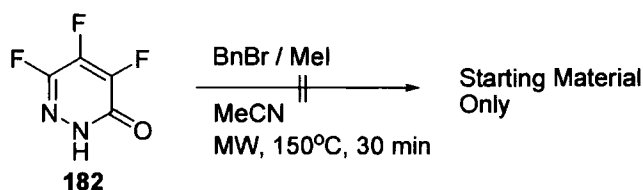


Scheme 3.2

However, the use of diazomethane presents a serious toxicity and explosion hazard, and its safe use requires specialist equipment. It was therefore decided to seek out alternative strategies for the *N*-alkylation of 4,5,6-trifluoropyridazin-3(2*H*)-one, and these are described in the forthcoming sections.

3.2 Attempted Alkylation of 4,5,6-Trifluoropyridazin-3(2*H*)-one

Attempted reaction of 4,5,6-trifluoropyridazin-3(2*H*)-one **182** with the strong alkylating agents benzyl bromide and methyl iodide in acetonitrile under microwave irradiation at 150°C returned only the starting material (Scheme 3.3). It can therefore be considered that the ring NH of 4,5,6-trifluoropyridazin-3(2*H*)-one **182** is not sufficiently nucleophilic to react with a range of alkyl halide electrophiles.



Scheme 3.3

A potential method of activating the pyridazin-3(2*H*)-one ring NH is by deprotonation with base to give a nitrogen anion, which will have higher nucleophilicity than the uncharged species. A range of bases were employed to effect the deprotonation, and several alkyl and acyl electrophiles were tested as potential trapping partners (Table 3.1). The electrophile was used in excesses up to 10 equivalents in an attempt to effect the desired transformation but, in all cases, a brown emulsion was obtained on aqueous workup that could not be dispersed on increasing salt concentration or sonication. The desired

alkylated product was observed in trace quantities (1-2 %) by GC-MS and the reaction mixture was complex and the major reaction components could not be identified.

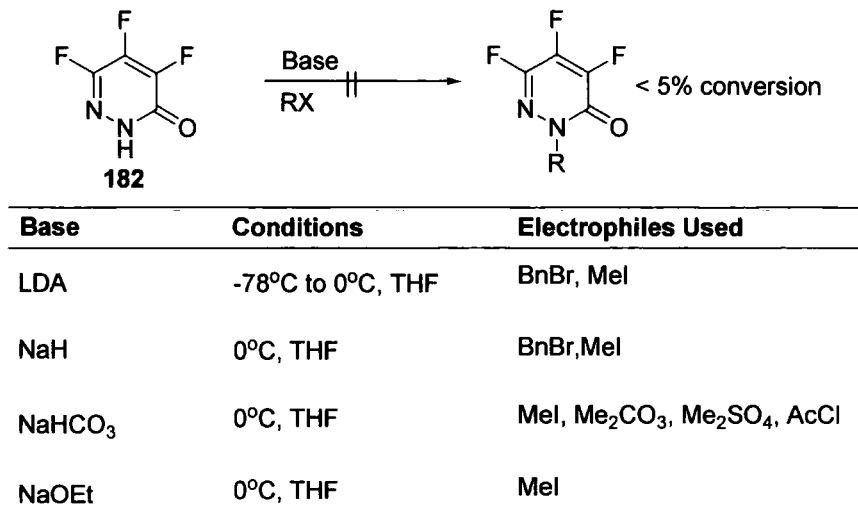


Table 3.1

It seems likely that the decomposition process observed with basic nucleophiles is occurring on deprotonation, and that this process is much more rapid than reaction with the electrophile, even when this is present in large excess.

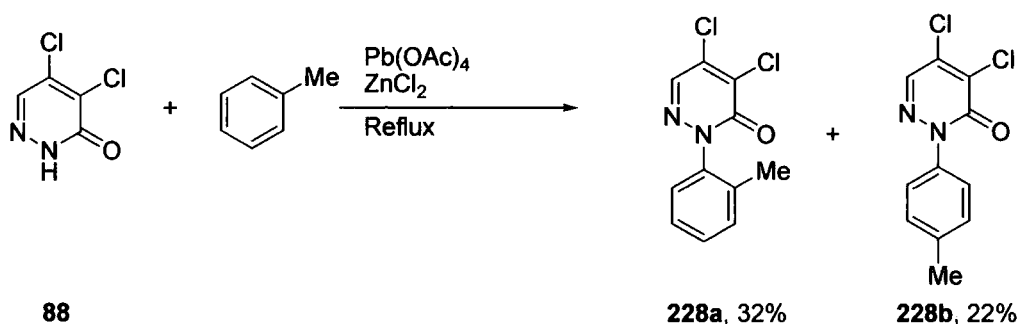
4,5,6-Trifluoropyridazin-3(2*H*)-one has been shown to be extremely base sensitive and it is incompatible with bases as weak as sodium hydrogen carbonate. Basic conditions should therefore be avoided in any *N*-functionalisation strategy.

3.3 *N*-Arylation of 4,5,6-Trifluoropyridazin-3(2*H*)-one

N-Arylated pyridazin-3(2*H*)-one derivatives are potentially very desirable systems as the introduction of an *N*-aryl group offers an additional point of molecular diversity, and many *N*-aryl oxy-heteroaromatics are known to be biologically active. Protection of the pyridazin-3(2*H*)-one ring NH by *N*-arylation is another potential solution to the difficulties encountered with the decomposition of 4,5,6-trifluoropyridazin-3(2*H*)-one in the presence of base.

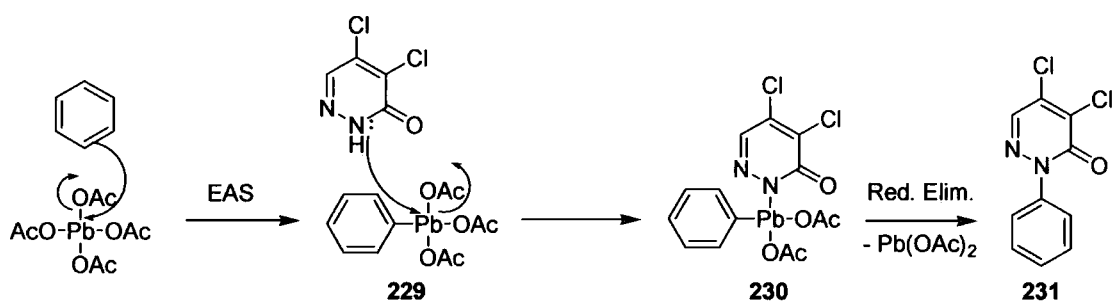
The *N*-arylation of various substituted pyridazin-3(2*H*)-one derivatives, including 4,5,6-trichloropyridazin-3(2*H*)-one and 4,5-dichloropyridazin-3(2*H*)-one **88**, has been

reported using lead (IV) acetate and a range of benzene derivatives (Scheme 3.4)¹⁵¹. The use of substituted benzene derivatives results in the formation of a mixture of *ortho* **228a** and *para* **228b** substituted regioisomers but if benzene itself is used as the coupling partner then a single *N*-phenylated product necessarily results.



Scheme 3.4

No mechanism was discussed but it is likely that this reaction proceeds *via* an aryllead intermediate **229** which undergoes nucleophilic displacement by the pyridazin-3(2*H*)-one ring NH to give a disubstituted organolead compound **230**, which can furnish the *N*-arylated product **231** by reductive elimination (Scheme 3.5). The role of the Lewis acid is likely to be in activating the acetate leaving groups on the organolead species. *Ortho*- and *para*-substituted products result from the initial *ortho*- and *para*-directed electrophilic substitution of lead tetracetate onto a substituted aromatic ring.



Scheme 3.5

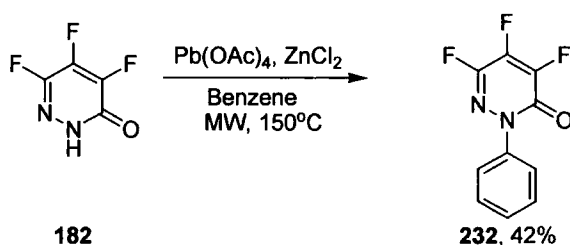
This process was examined as a possible strategy for the *N*-arylation of 4,5,6-trifluoropyridazin-3(2*H*)-one **182** where benzene was chosen as the coupling partner. Conditions were screened to optimise the conversion of this reaction, in which

stoichiometry of lead(IV) acetate, zinc(II) chloride, as well as temperature and time were varied (Table 3.2). Microwave irradiation was used to allow rapid optimisation of conditions. Lead(IV) acetate (1.5 equivalents) and zinc(II) chloride (1.0 equivalents) were found to be optimal, but an increase in the reaction time or temperature had minimal effect on conversion. Conversions, which were determined by integration of crude ^{19}F NMR spectra, were slightly reduced under standard thermal reflux conditions.

Equiv Pb(OAc) ₄	Equiv ZnCl ₂	Temp / °C	Time / min	Conversion
1.1	1.0	150	5	49
1.5	1.0	150	5	64
2.0	1.0	150	5	46
1.1	1.5	150	5	52
1.1	2.0	150	5	51
1.5	1.0	150	10	63
1.5	1.0	160	5	64
1.5	1.0	170	5	58
1.5	1.0	Reflux	960	55

Table 3.2

The reaction was scaled up to a 2g scale and the desired *N*-arylated product **232** isolated in moderate yield (Scheme 3.6). Separation from the starting material and metal salts was carried out effectively by flash column chromatography on silica gel, which allowed unreacted starting material to be recycled.



Scheme 3.6

Nucleophilic aromatic substitution processes of the *N*-phenyl pyridazin-3(2*H*)-one **232** were studied to examine its reactivity and to determine whether the aryl substituent affected regioselectivity. Sodium methoxide, benzylamine and morpholine were chosen as representative examples of alkoxide, primary amine and secondary amine nucleophiles respectively. As for the unprotected pyridazin-3(2*H*)-one, substitution reactions were carried out at room temperature in acetonitrile, using the same concentration ($3.33 \mu\text{mol dm}^{-3}$) to allow direct comparisons between the protected and unprotected compounds to be drawn. The exception to this methodology was the reaction with sodium methoxide, with which methanol was used as solvent to improve solubility of the nucleophile.

Nucleophile	Yield 4- Isomer ^a	Yield 5- Isomer ^a	Ratio 4:5- Isomers ^b
NaOMe ^c 233a*	 233b , 64%	7 : 93	
 234a , 40%	 234b , 30%	60 : 40	
 235a , 58%	 235b*	85 : 15	

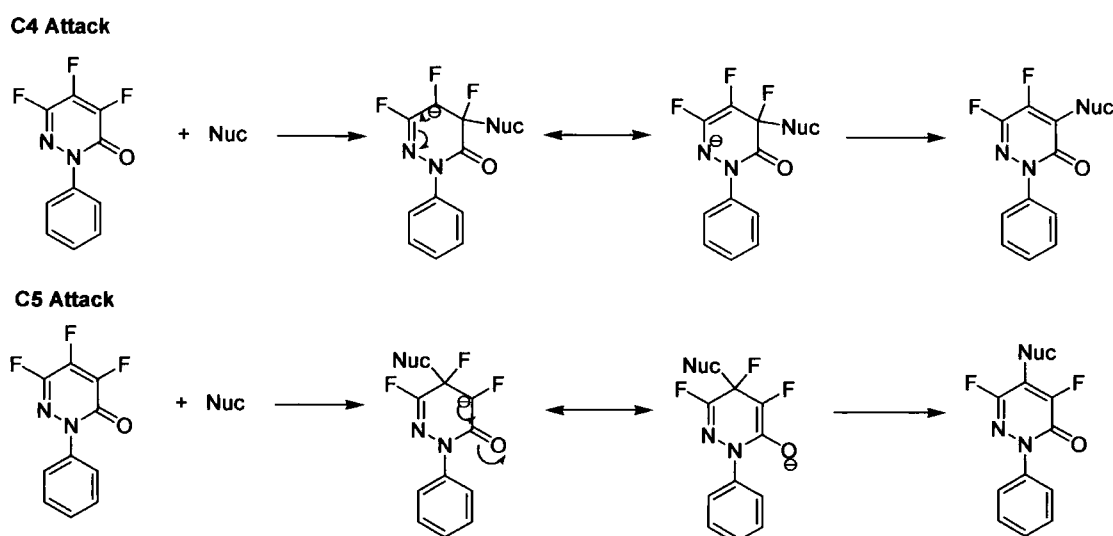
^a Isolated Yields^b Isomer ratios determined by integration of crude ^{19}F NMR spectra^c Solvent used was methanol

* Not isolated

Table 3.3

The isomer ratios obtained with primary amines suggest that the *N*-phenyl substituent has a minimal influence on the reactivity of the system by comparison to results obtained for nucleophilic substitution reactions of unprotected 4,5,6-trifluoropyridazin-3(2*H*)-one using the same nucleophiles and under identical conditions. For example, for benzylamine the ratio of regioisomers is virtually unchanged between the unarylated and *N*-phenylated pyridazin-3(2*H*)-ones (60 : 40 *N*-phenyl vs. 61 : 39 unarylated), whilst with morpholine selectivity is marginally increased (85 : 15 *N*-phenyl vs. 77 : 23 unarylated), although this is not significantly different.

A significant change in regioselectivity on *N*-arylation would not be expected because it is not possible to stabilise the negative charge that develops in the Meisenheimer intermediates resultant from attack at either C4 or C5 by delocalisation onto the phenyl ring (Scheme 3.7).



Scheme 3.7

N-Phenylation allowed the reaction of basic oxygen nucleophiles with the trifluoropyridazin-3(2*H*)-one ring system to proceed in high conversion. The use of sodium methoxide as nucleophile afforded the 5-methoxy compound **233b** as major product with high regioselectivity (7 : 93). This is the opposite major product to that obtained with amines, which favoured substitution at the 4-position. This supports the hypothesis described in the previous chapter that the 5-position is the ‘harder’ site electronically and reacts preferentially with hard nucleophiles, whereas the 4-position is ‘softer’ and reacts

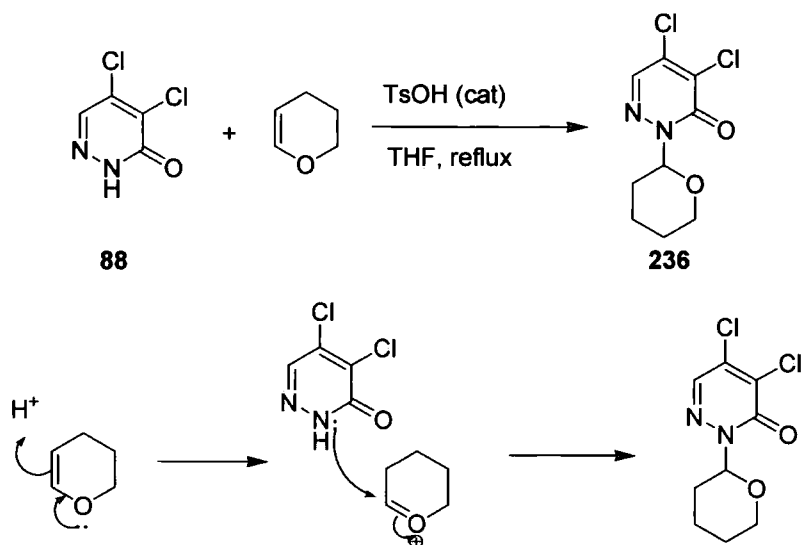
with soft nucleophiles. Oxygen nucleophiles are much harder than amines, so demonstrate high regioselectivity for attack at the 5-position.

N-Phenylation has been shown to allow the reaction of 4,5,6-trifluoropyridazin-3(2*H*)-one with nucleophiles more basic than amines, such as alkoxides, as planned in the strategy. However, the procedure described here is not ideal for all applications. The use of toxic reagents such as lead tetraacetate and benzene will be discouraging to highly regulated industries, such as pharmaceuticals. Also, whilst *N*-arylation gives biologically interesting *N*-phenyl-pyridazin-3(2*H*)-ones, it is not possible to remove the *N*-aryl group if a pyridazin-3(2*H*)-one unsubstituted at nitrogen is desired. Consequently, other *N*-protecting groups were sought.

3.4 *N*-Protected Pyridazin-3(2*H*)-ones

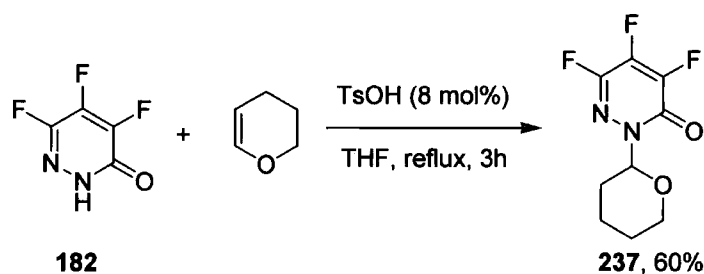
To allow the synthesis of oxygen containing pyridazin-3(2*H*)-ones that are not functionalised at ring nitrogen, a readily removable protecting group was sought. Such a protecting group should not require basic conditions for its introduction, as the base sensitivity of 4,5,6-trifluoropyridazin-3(2*H*)-one will most likely lead to its decomposition. The protecting group should not affect the reactivity of the pyridazin-3(2*H*)-one ring too dramatically, should be able to be removed under mild conditions and must also be compatible with the necessarily basic conditions required in nucleophilic displacements. Consequently, protecting group introduction and removal under acidic conditions would be advantageous.

Many standard amine protecting groups such as BOC, Fmoc, CBz and benzyl require basic conditions for their introduction. However, the tetrahydropyranyl group (THP), whilst traditionally known as an alcohol protecting group, is introduced using mildly acidic conditions and removed under more strongly acidic conditions. THP protection at the ring NH of pyridazin-3(2*H*)-ones has been previously reported for the preparation of the *N*-tetrahydropyranyl derivative of 4,5-dichloropyridazin-3(2*H*)-one (Scheme 3.8)¹⁵².



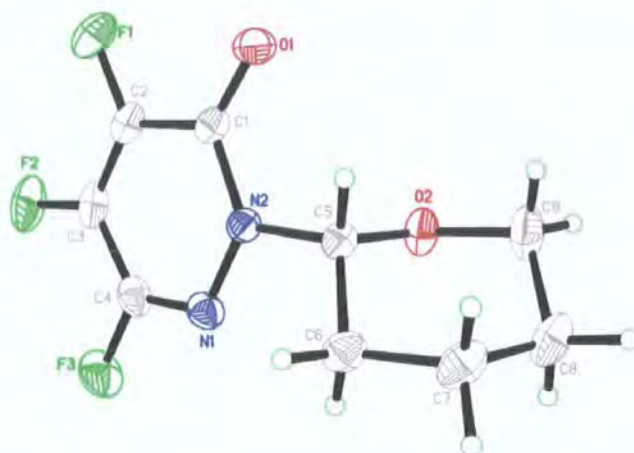
Scheme 3.8

We envisaged that an analogous procedure could provide a suitable strategy for the protection of 4,5,6-trifluoropyridazin-3(2*H*)-one **182** as its *N*-tetrahydropyranyl derivative. Reaction of 4,5,6-trifluoropyridazin-3(2*H*)-one with 3,4-dihydropyran in the presence of catalytic (8 mol%) *p*-toluenesulfonic acid yielded the desired 4,5,6-trifluoro-2-(tetrahydropyran-2-yl)pyridazin-3(2*H*)-one **237** in good yield (Scheme 3.9). An optimal reflux period of 3 hours was observed, shorter periods resulted in incomplete conversion, whilst longer reaction times provided an increased amount of an unidentified by-product.



Scheme 3.9

X-ray crystallography was used to confirm that protection had, indeed, occurred on the ring nitrogen, as opposed to the carbonyl oxygen (Figure 3.1). The use of the tetrahydropyranyl group as a nitrogen protecting group is relatively unusual, but its chemical properties make it ideal for our purpose.



Bond	Bond Length / Å
C(1)-O(1)	1.2202
N(1)-C(4)	1.2751
N(2)-C(1)	1.3893
N(1)-N(2)	1.3596

Bond	Bond Angle / °
N(2)-C(1)-C(2)	113.31
O(1)-C(1)-N(2)	122.93
C(1)-N(2)-N(1)	125.59
O(1)-C(1)-C(2)	123.76

Figure 3.1: X-ray Crystal Structure of 4,5,6-trifluoro-2-(tetrahydro-2*H*-pyran-2-yl)-pyridazin-3(2*H*)-one **237**

4,5,6-Trifluoro-2-(tetrahydro-2*H*-pyran-2-yl)pyridazin-3(2*H*)-one **237** was then examined as a potential scaffold for sequential nucleophilic aromatic substitution reactions to determine the effect of *N*-alkylation on these processes (Table 3.4). The standard range of alkoxide and primary, secondary and aromatic amine nucleophiles were reacted under standard conditions, namely by stirring at room temperature in acetonitrile at a concentration of $3.33 \mu\text{mol dm}^{-3}$. These conditions are identical to those used in the monosubstitution reactions of 4,5,6-trifluoropyridazin-3(2*H*)-one, allowing direct comparisons to be drawn between the reactivity of the protected and unprotected derivatives. Products were identified as described previously in Chapter 2 by analysis of ^{13}C NMR J_{CF} coupling constants.

The stability of the THP protecting group was shown to be high under the reaction conditions and the products were stable to column chromatography on silica. The one exception observed to this was in the reaction of *N*-THP-4,5,6-trifluoropyridazin-3(2*H*)-one with *p*-anisidine, with which a significant amount of the deprotected substituted product **196a** was observed. This is likely to be because *p*-anisidine is the weakest base of the

nucleophiles examined and so is the least effective at neutralising the HF formed as by-product. If HF accumulates this could lead to deprotection of the THP group.

Nucleophile	Yield 4- isomer ^a	Yield 5- isomer ^a	Yield Disubstituted ^a	Ratio 4: 5: Di- Isomers ^b
	 238a , 46%	 238b , 34%	-	55 : 45 : 0
	 239a*	-	 239c , 45%	12 : 0 : 88
	-	-	-	
	 240a , 20% ^d	-	-	>95 : 0 : 0
	-	 241b*	 241c , 55%	0 : 15 : 85
	-	 242b*	 242c , 35%	0 : 34 : 66

^a Isolated yields

^b Isomer ratios determined by integration of crude ¹⁹F NMR spectra

^c No conversion - starting material returned

^d A significant amount of substituted, deprotected compound formed (protected : deprotected 40 : 60)

^e Solvent used was THF

* Not isolated

Table 3.4

The results obtained with butylamine again suggest that the substitution of the ring NH has a minimal effect on the selectivity of attack (55 : 45 protected *vs.* 57 : 43 unprotected). Similarly, the use of aniline derivatives favours substitution at the 4-position with high regioselectivity. Indeed, in this case, the use of *p*-anisidine resulted in substitution at the 4-position exclusively, with no 5-substituted isomer being detected in the crude ^{19}F NMR of the reaction mixture.

However, with more reactive amine nucleophiles, such as morpholine, a tendency to form the disubstituted product was observed. This was unexpected, as it was thought that the presence of a second equivalent of amine nucleophile was required to neutralise the HF by-product of the reaction, so it was thought reaction with two equivalents of amine could only result in monosubstitution. However, various other basic sites are available, including amines on the product, and even the solvent acetonitrile is mildly basic.

The reaction of alkoxide nucleophiles with this protected system was again feasible, and again reaction with two equivalents of nucleophile resulted in formation of mainly the disubstituted products.

To obtain monosubstitution more selectively, the stoichiometry of the reaction was reduced to one equivalent of nucleophile in the reactions that gave significant amounts of disubstitution (Table 3.5). This resulted in the formation of mainly the desired monosubstituted products, although with alkoxide nucleophiles trace amounts of disubstituted products were again observed. The ratio of monosubstituted isomers obtained with morpholine was again similar to that obtained using the unprotected pyridazin-3(2H)-one (71 : 29 protected *vs.* 77 : 23 unprotected), demonstrating that NH protection has a minimal influence on regioselectivity.

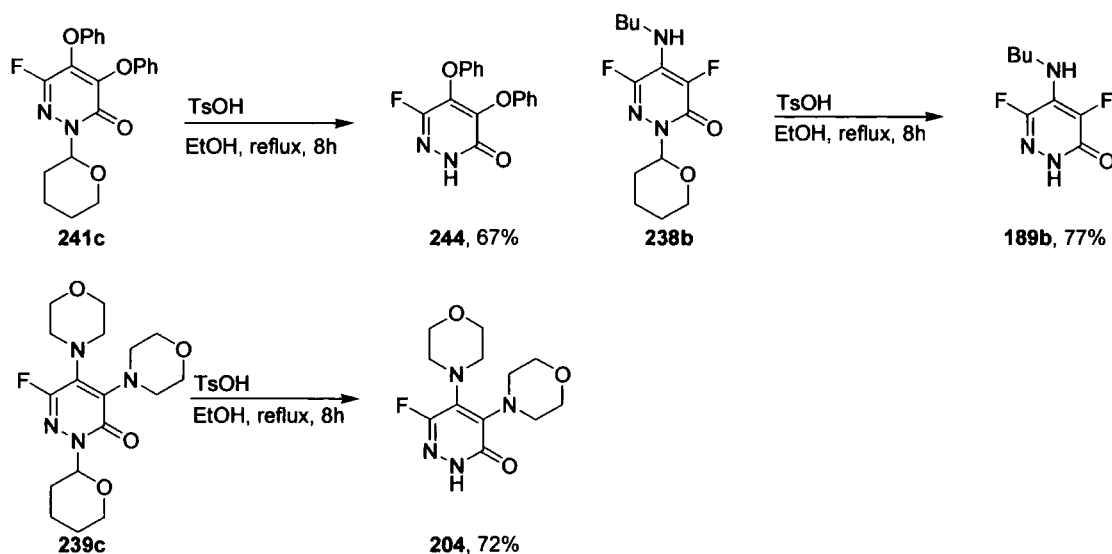
The major monosubstituted isomer obtained using alkoxide nucleophiles has been shown to be substituted at the 5-position. This is also in agreement with the hypothesis that this is the harder site electronically, as it is *ortho* to two highly electronegative C-F bonds.

Nucleophile	Conversion / %	Yield 4- isomer ^a	Yield 5- isomer ^a	Yield Disubstituted ^a	Ratio 4:5:Di- Products ^b
	88	 239a , 58%	 239b*	-	71 : 29 : 0
NaOEt	91	 243a*	 243b , 68%	 243c*	7 : 80 : 13

^a Isolated Yields
^b Isomer ratios determined by integration of crude ¹⁹F NMR spectra
^c Solvent used was EtOH
 * Not Isolated

Table 3.5

Deprotection of the THP group occurs readily under standard acidic THP deprotection conditions (Scheme 3.10). Thus, reflux of a range of oxygen and nitrogen substituted *N*-THP pyridazin-3(2*H*)-ones in the presence of stoichiometric *p*-toluenesulfonic acid in ethanol yielded the NH deprotected pyridazin-3(2*H*)-one in high yield. This strategy provides an efficient route to the unprotected pyridazin-3(2*H*)-ones, particularly those functionalised with oxygen substituents (e.g. **244**).



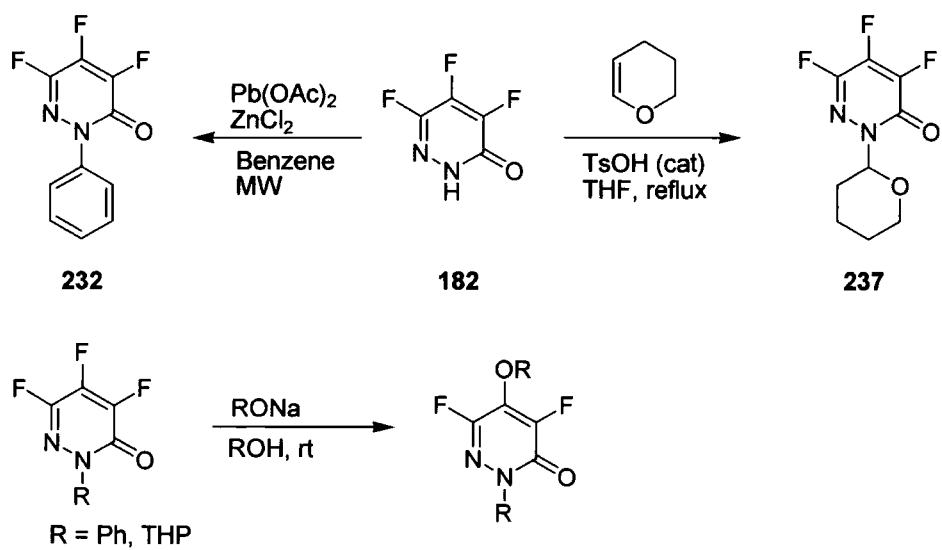
Scheme 3.10

3.5 Conclusions

Functionalisation of the acidic ring NH allows the range of potential nucleophiles compatible with these systems to be expanded to include nucleophiles of high basicity, such as alkoxides (Scheme 3.11). This has increased the potential substituent diversity that can be introduced into this system.

Simple alkylation does not proceed due to the sensitivity of 4,5,6-trifluoropyridazin-3(2*H*)-one towards base, however *N*-functionalisation is feasible using a lead-mediated arylation reaction, or by acid catalysed THP protection.

N-Protection does not alter the reactivity of the pyridazin-3(2*H*)-one scaffold significantly, so similar ratios of isomers are obtained with and without protection. The use of alkoxide nucleophiles favours attack at the harder 5-position of the pyridazin-3(2*H*)-one ring, compared to softer amine nucleophiles which favour attack at the 4-position.



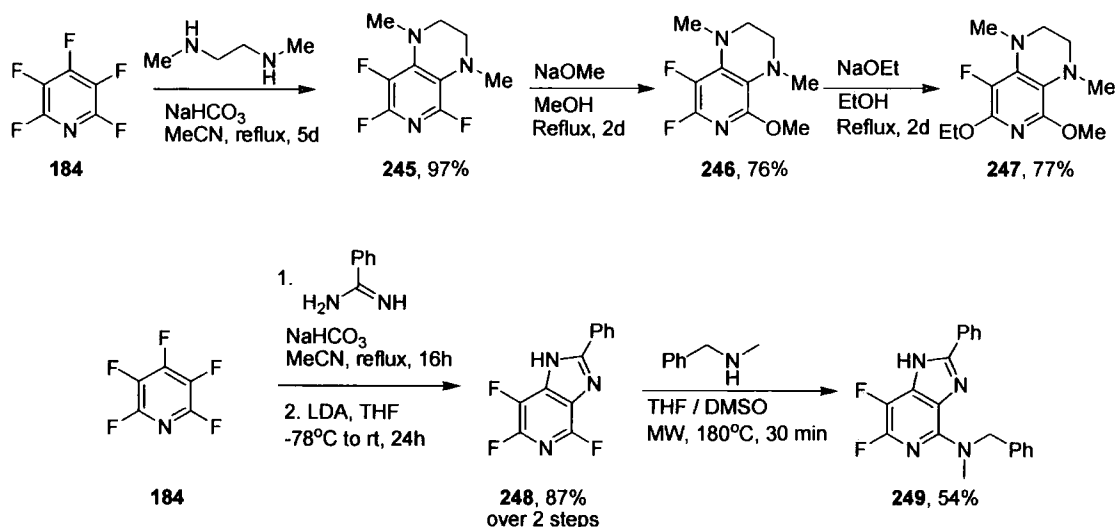
Scheme 3.11

Chapter 4

Syntheses of Ring-Fused Pyridazine Systems from Tetrafluoropyridazine

4.1 Introduction

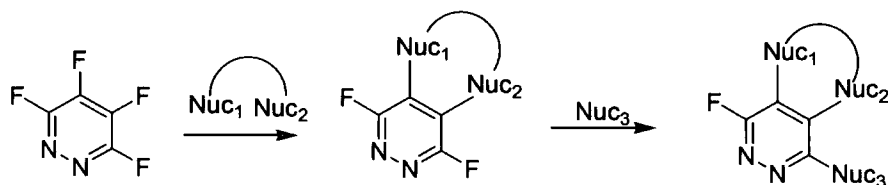
Reactions of perfluorinated heteroaromatics with dinucleophilic species have the potential to yield ring fused systems. Previous work in the Durham group has been directed towards the synthesis of fused pyridine systems by reaction of pentafluoropyridine **184** and substituted tetrafluoropyridine compounds with appropriate dinucleophiles including ethylene diamine and amidine derivatives (Scheme 4.1)¹⁵³⁻¹⁵⁵. The ring fused scaffolds produced possessed fluorine atoms which were also susceptible to displacement by nucleophiles to introduce substituent diversity.



Scheme 4.1

It can be envisaged that reaction of tetrafluoropyridazine with dinucleophiles should allow for the synthesis of ring fused pyridazine systems in a similar fashion. Again, displacement of the remaining fluorine atoms after annelation would yield substituted systems, allowing both skeletal and substituent diversity to be developed from a simple precursor (Scheme 4.2).





Scheme 4.2

4.2 Reactions of Tetrafluoropyridazine with 1,2-Dinucleophiles

1,2-Dinucleophiles are species with nucleophilic functionality on adjacent carbon atoms, such as diamines, diols and dithiols, and would be expected to yield [6,6]-ring fused products on reaction with tetrafluoropyridazine. Examples of commercially available 1,2-dinucleophiles are shown in Figure 4.1.

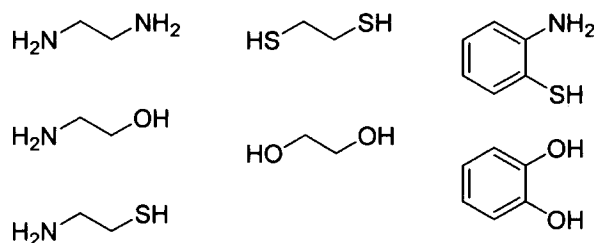
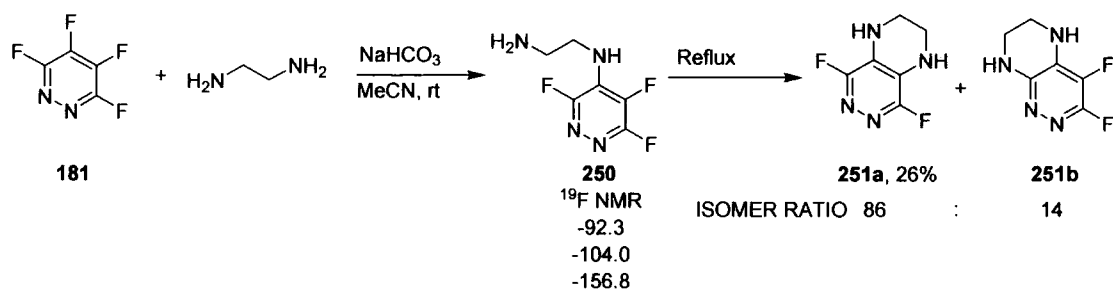


Figure 4.1

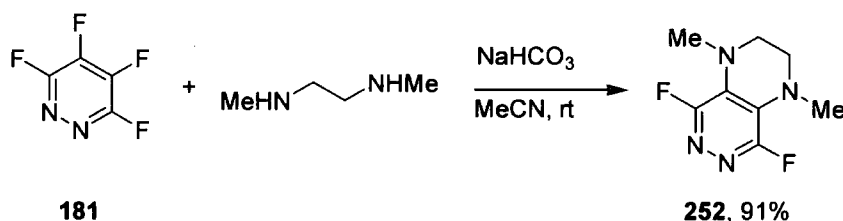
4.2.1 Nitrogen Containing 1,2-Dinucleophiles

Reaction of tetrafluoropyridazine **181** with ethylenediamine (Scheme 4.3) gave an uncyclised amine derivative **250** at room temperature, which was not isolated but was observed by ¹⁹F NMR. The intermediate product underwent cyclisation on heating to give a mixture of two ring fused systems, the major regioisomer **251a** being cyclised at the 4- and 5-positions, with a small amount (14% of the crude reaction mixture by ¹⁹F NMR) of the 3,4-cyclised derivative **251b**. The major product was identified by the observation of only one resonance in its ¹⁹F NMR spectrum and similar equivalences in its ¹H and ¹³C NMR spectra due to its symmetry.



Scheme 4.3

Use of a secondary diamine derivative, *N,N'*-dimethylethylenediamine, yields the 4,5-cyclised product **252** exclusively in good yield (Scheme 4.4). In this case the reaction proceeds at room temperature and uncyclised product is not observed on monitoring the reaction by ^{19}F NMR.



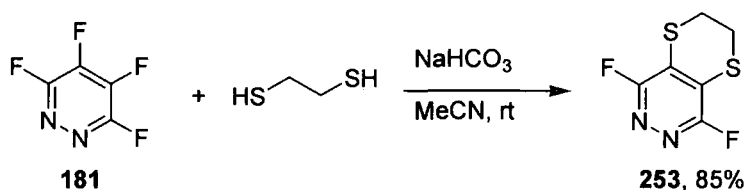
Scheme 4.4

The increased selectivity in the case of *N,N'*-dimethylethylenediamine is most likely due to the milder reaction conditions required to achieve cyclisation, ensuring that the kinetic product is formed exclusively *via* reaction at the two most activated sites *para* to ring nitrogen. At reflux temperature, which is required to achieve cyclisation using the less nucleophilic ethylenediamine, some of the 3,4-cyclised product **251b** is formed which is likely to be more thermodynamically stable for steric reasons. Less selectivity is observed at higher reaction temperatures.

It would appear reasonable to suggest that these cyclisations proceed *via* initial nucleophilic attack of a single amine, followed by an intramolecular 6-*exo-trig* cyclisation of the second nucleophilic group preferentially onto the most activated site *para* to ring nitrogen, which also has an activating *ortho*-fluorine.

4.2.2 Sulfur Containing 1,2-Dinucleophiles

Similarly to the reactions with diamine derivatives, reaction of tetrafluoropyridazine with ethane-1,2-dithiol yields a symmetrical cyclised derivative **253** as a single regioisomer at room temperature in acetonitrile (Scheme 4.5). The use of reactive thiol nucleophiles ensure that the reaction proceeds efficiently and that no uncyclised product is observed by ^{19}F NMR analysis.



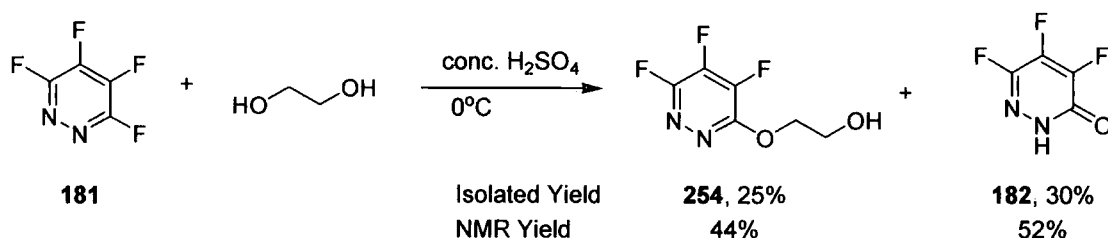
Scheme 4.5

4.2.3 Oxygen Containing 1,2-Dinucleophiles

Diols were not sufficiently nucleophilic to react with tetrafluoropyridazine, even at reflux temperature, for example, reflux of ethylene glycol with tetrafluoropyridazine in THF returned only the starting materials. Therefore, activation of either the tetrafluoropyridazine electrophile or the diol nucleophile is required to achieve substitution.

It is known that, in the presence of concentrated strong acid, protonation of tetrafluoropyridazine occurs at ring nitrogen to form the tetrafluoropyridazinium cation¹³³, which has been shown to react with oxygen nucleophiles at the 3-position and this approach was used in the synthesis of 4,5,6-trifluoropyridazin-3(2*H*)-one. It could, therefore, be envisaged that reaction of tetrafluoropyridazine with a diol in concentrated sulfuric acid could lead to substitution at the 3-position.

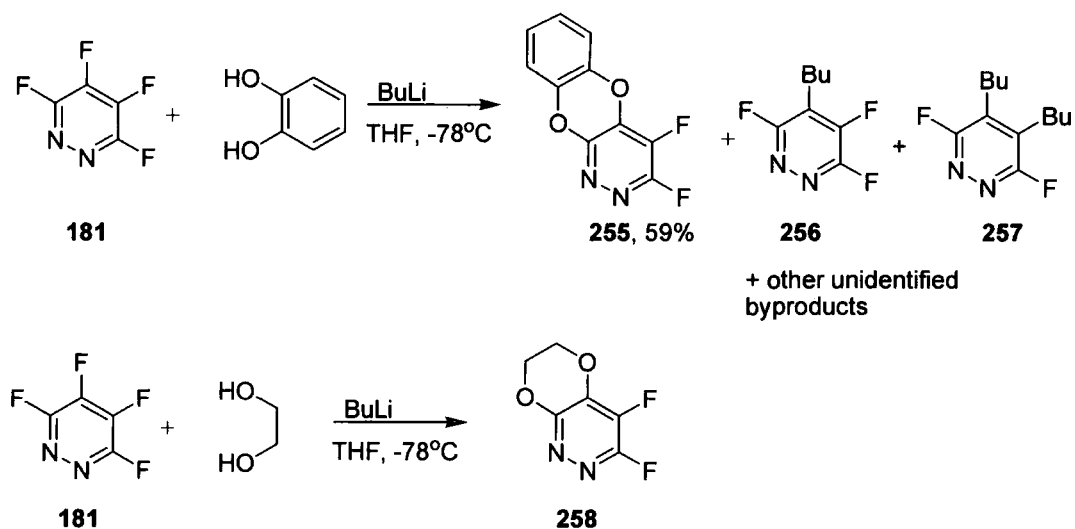
This was indeed the case on reaction of tetrafluoropyridazine with ethylene glycol in concentrated sulfuric acid which yielded a 3-substituted pyridazine **254**, but a significant amount of 4,5,6-trifluoropyridazin-3(2*H*)-one **182** was also produced in the reaction, formed by hydrolysis from water present in the sulfuric acid (Scheme 4.6).



Scheme 4.6

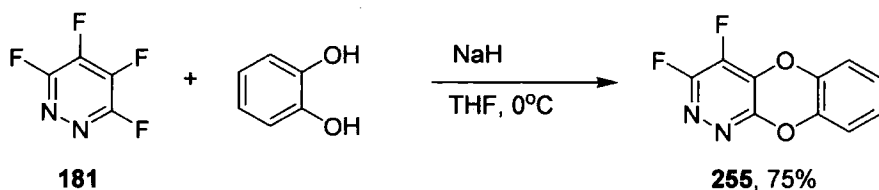
The uncyclised alcohol could most likely be transformed into the annulated derivative by reaction with strong base to achieve deprotonation, but the low yield precluded development of this strategy.

An alternative strategy for the synthesis of cyclised derivatives by reaction of tetrafluoropyridazine with diols is *via* activation of the nucleophile by deprotonation with strong base. This was achieved initially using *n*-BuLi to deprotonate ethylene glycol and catechol (Scheme 4.7). Annulated products **255** and **258** were obtained but nucleophilic attack by Bu[−] was also observed in significant amounts, rendering the reaction mixture relatively complex.



Scheme 4.7

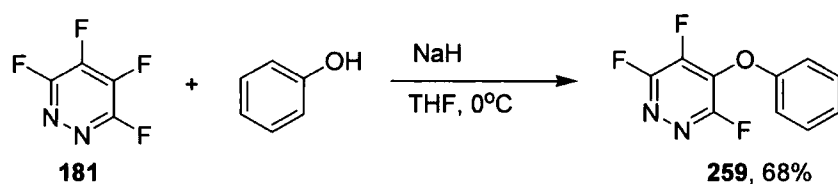
The formation of these by-products was prevented by the use of sodium hydride as base, which is non-nucleophilic and in this case the cyclic derivative **255** was produced in good yield (Scheme 4.8).



Scheme 4.8

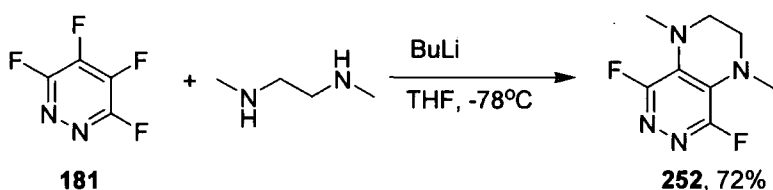
It should be noted that the cyclic derivative **255** produced in this case had undergone annulation between the 3- and 4-positions, the opposite regioisomer to that observed with nitrogen and sulfur nucleophiles. This was confirmed by the lack of symmetry observed in its NMR spectra, displaying two separate ^{19}F resonances at -96 ppm, characteristic of fluorine *ortho* to ring nitrogen, and -152 ppm that is not deshielded by *ortho* ring nitrogen.

To probe the mechanism of this unexpected result, tetrafluoropyridazine was reacted with sodium phenoxide to determine whether initial nucleophilic attack occurred at the 3- or 4-positions with oxygen nucleophiles. The 4-phenoxy derivative **259** was produced selectively (Scheme 4.9), suggesting that these reactions proceeded *via* initial nucleophilic attack at the 4-position, followed by cyclisation onto the 3-position. The regiochemistry of this product was confirmed by examination of its ^{19}F NMR spectrum, which showed the presence of two fluorine atoms deshielded by the *ortho* ring nitrogen at -86 and -95 ppm and a fluorine resonance at -140 ppm that is not *ortho* to ring nitrogen.



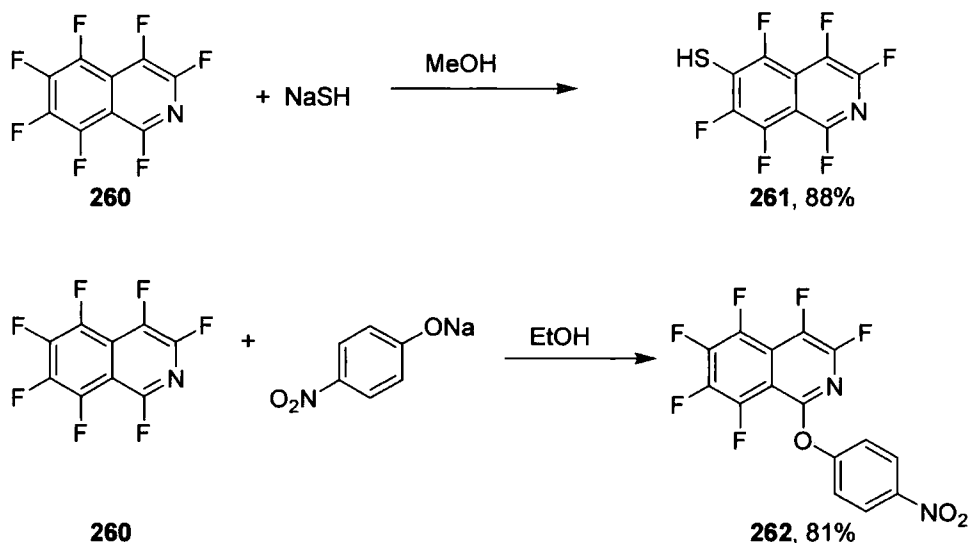
Scheme 4.9

To examine whether potential coordination of the basic pyridazine ring nitrogen to the cation of the salt is directing the regioselectivity of this process the reaction of tetrafluoropyridazine with N,N'-dimethylethylenediamine in the presence of *n*-BuLi was performed (Scheme 4.10). This simply yielded the 4,5-cyclised product **252** as was the case in the absence of strong base which does not support potential coordination of the cation to the ring nitrogen directing substitution to the site *ortho* to itself.



Scheme 4.10

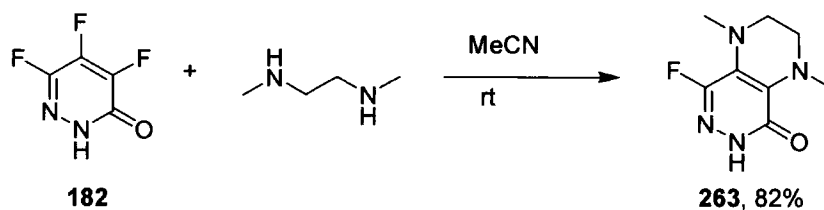
The difference in regioselectivity observed with oxygen dinucleophiles is therefore most probably an electronic effect, in that the ‘hard’ oxygen anion cyclises preferentially at the ‘hardest’ site of the pyridazine ring. It is well established that the sites *ortho* to electronegative ring nitrogen in perfluorinated heteroaromatics are the hardest sites, and examples of preferential reaction of oxygen nucleophiles at these sites are known in the literature. For example, perfluoroisoquinoline **260** reacts selectively with sulfur nucleophiles at the 6-position to give **261**, whilst harder oxygen nucleophiles undergo regioselective substitution at the 1-position, *ortho* to ring nitrogen, to produce **262** (Scheme 4.11)¹⁵⁶.



Scheme 4.11

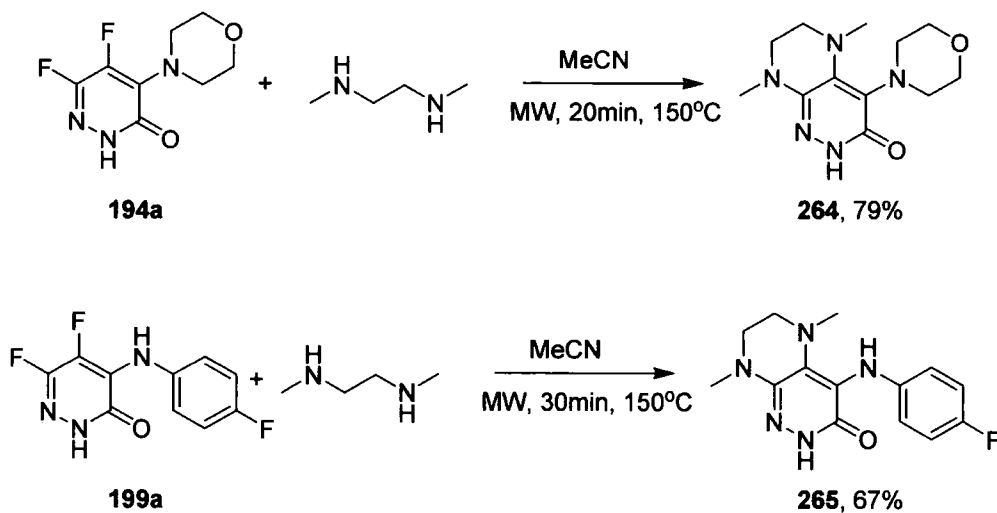
4.2.4 Reactions of 4,5,6-Trifluoropyridazin-3(2H)-one with Dinucleophiles

4,5,6-Trifluoropyridazin-3(2H)-one **182** was reacted with N,N'-dimethylethylenediamine under analogous conditions to those used with tetrafluoropyridazine to yield a single [6,6]-ring fused product **263** regioselectively, formed by cyclisation between the 4- and 5-positions (Scheme 4.12).



Scheme 4.12

Two 4-substituted difluoropyridazin-3(2H)-ones were also reacted with N,N'-dimethylethylenediamine under microwave irradiation, which lead to replacement of both remaining fluorine atoms to provide non-halogenated products **264** and **265** (Scheme 4.13). The structure of **264** was confirmed by X-ray crystallography (Figure 4.2) and showed the presence of hydrogen bonded dimers interlinked into chains by π -stacking interactions in the solid state.



Scheme 4.13

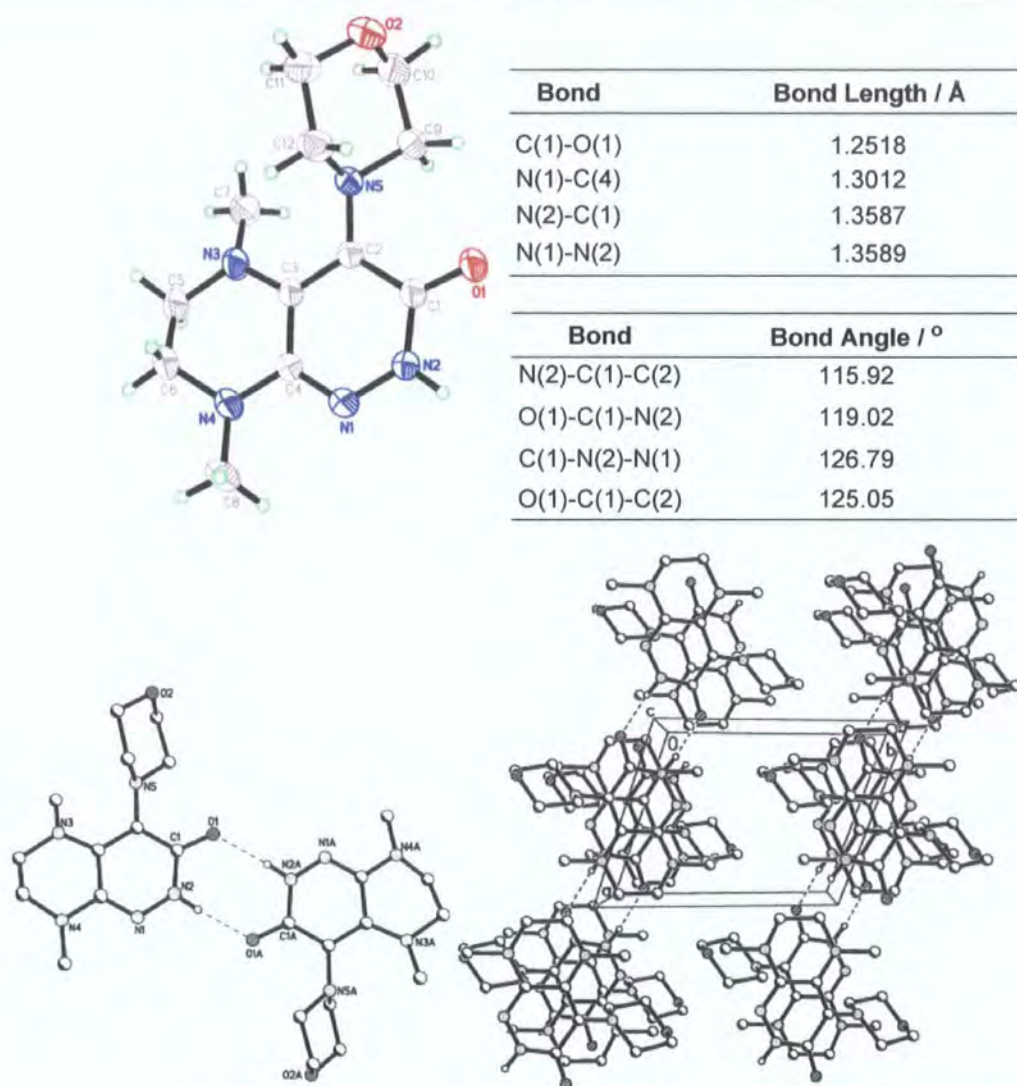


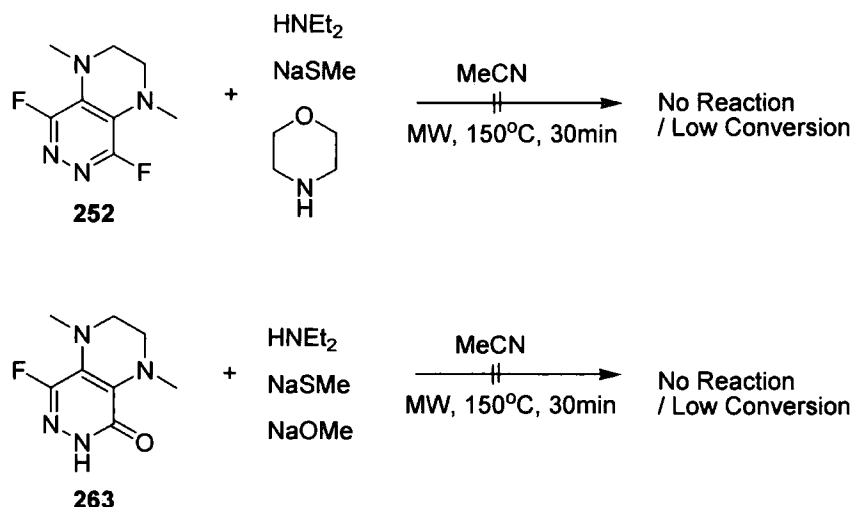
Figure 4.2: X-ray Crystal Structure of 5,6,7,8-tetrahydro-5,8-dimethyl-4-morpholinopyrazino[2,3-*c*]pyridazin-3(2*H*)-one **264**

These reactions demonstrated that displacement of the final ring fluorine in pyridazin-3(2*H*)-one systems is feasible if the final displacement is an entropically favourable intramolecular reaction. As discussed earlier, 4,5-disubstituted 6-fluoropyridazin-3(2*H*)-one derivatives were unreactive towards displacement of the final ring fluorine in intermolecular displacement reactions under the conditions described in Chapter 2.

4.3 Reactions of [6,6]-Ring Fused Scaffolds with Nucleophiles

The [6,6]-ring fused products that arise from reaction of tetrafluoropyridazine and 4,5,6-trifluoropyridazin-3(2*H*)-one with 1,2-dinucleophiles have remaining fluorine atoms on their aromatic ring, so have the potential to participate in further nucleophilic aromatic substitution reactions. Reactions with primary, secondary and aromatic amines, alkoxide and thiolate nucleophiles were explored to determine the scope for further functionalisation.

Both 5,8-difluoro-1,2,3,4-tetrahydro-1,4-dimethylpyrazino[2,3-*d*]pyridazine **252** and 8-fluoro-1,2,3,4-tetrahydro-1,4-dimethylpyrazino[2,3-*d*]pyridazin-5(6*H*)-one **263** proved to be unreactive towards further nucleophilic displacement reactions under the microwave irradiation conditions examined. Generally, only starting material was observed on analysis of the crude reaction mixture by LC-MS, however low conversions to the substituted products (< 20%) were observed in the case of reactive thiolate nucleophiles, although the substituted derivatives could not be isolated.

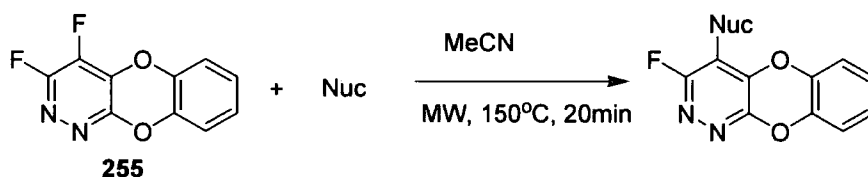


Scheme 4.14

It is likely that in this case replacement of two electron-withdrawing fluorine atoms by two less activating nitrogen atoms deactivate the system sufficiently to make further substitution reactions difficult.

The product of substitution of tetrafluoropyridazine by catechol **255** was also reacted with a range of nucleophilic species under microwave irradiation and in this case

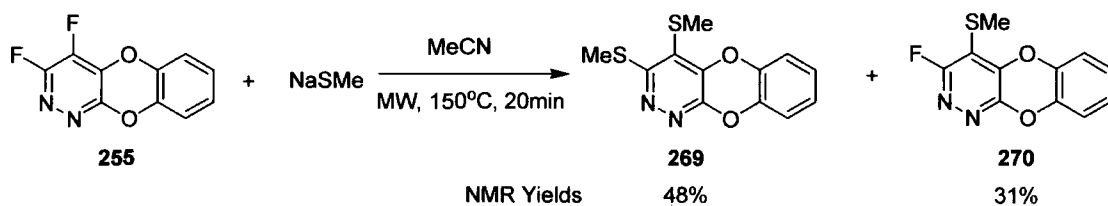
substituted derivatives were isolated in good yield with primary and secondary amines, as well as with the alkoxide nucleophile sodium methoxide (Table 4.1). 4-Fluoroaniline was not sufficiently nucleophilic to react under these conditions, whilst sodium methanethiolate gave a complex mixture of mono- (**270**) and di- (**269**) substituted products that were inseparable (Scheme 4.15).



Nucleophile	Product	Isolated Yield / %
	 266	71
	 267	80
		0*
NaOMe	 268	66

* Starting Material Returned

Table 4.1



Scheme 4.15

Examination of the ^{19}F chemical shifts of the substituted derivatives suggested that substitution had occurred at the 4-position, as the chemical shift of the remaining fluorine atom ranged from -86 to -93 ppm, which is characteristic of fluorine deshielded by adjacent ring nitrogen.

A crystal structure of the 5-allylamino derivative **267** (Figure 4.3) confirmed both that these compounds underwent selective substitution at the 5-position, and that annulation had previously occurred between the 3- and 4-positions of the pyridazine ring in reaction with catechol. Again, networks held together in the solid state by hydrogen bonding and π -stacking were observed.

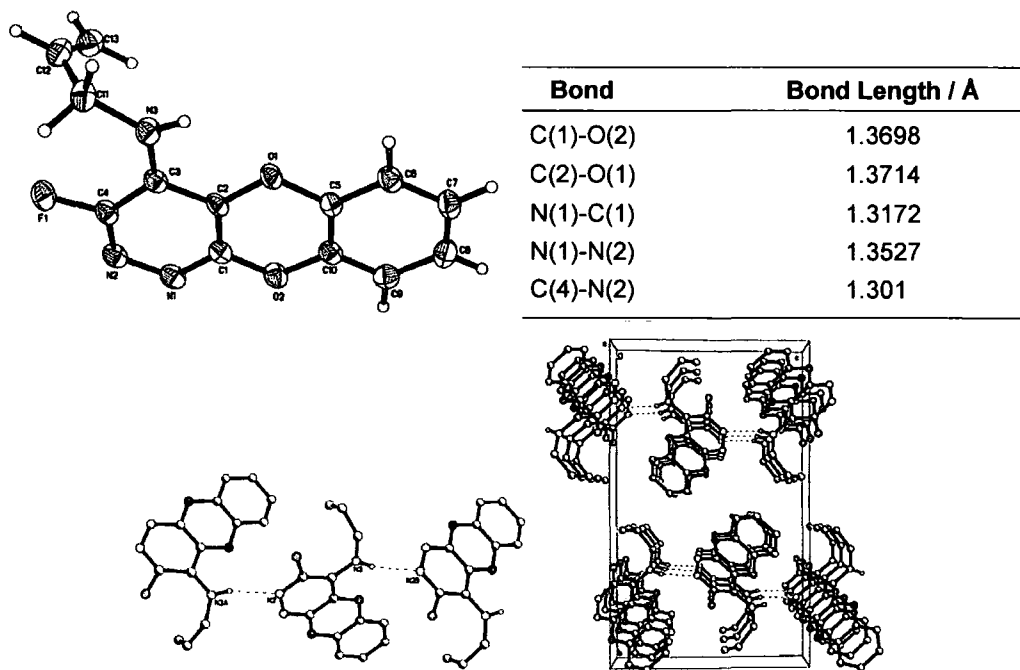
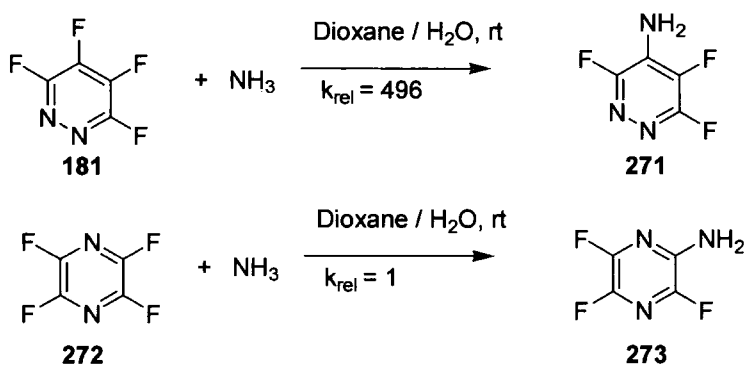


Figure 4.3: X-ray Crystal Structure of 3-Fluoro-4-allylamino-9,10-dioxo-1,2-diazaphenanthrene **267**

The dioxygenated annulated **255** derivative undergoes regioselective substitution at the 5-position of the pyridazine ring, *para* to activating ring nitrogen. It is likely that these derivatives are more reactive than the dinitrogen fused systems as oxygen is both more electronegative and a less effective electron donor than nitrogen. Also, the 3,4-dioxygen cyclised scaffold possesses a more reactive C-F bond *para* to activating ring nitrogen, whilst the 4,5-dinitrogen cyclised scaffolds possess only less activated C-F bonds *ortho* to ring nitrogen. This activating effect of *para* ring nitrogen is demonstrated in the increased reactivity of tetrafluoropyridazine **181** relative to tetrafluoropyrazine **272** ($k_{\text{pyridazine}} / k_{\text{pyrazine}} \sim 500$), which has no fluorine atoms *para* to ring nitrogen (Scheme 4.16)¹⁵⁷.



Scheme 4.16

4.4 Reactions of Tetrafluoropyridazine with 1,1-Dinucleophiles

1,1-Dinucleophiles possess two nucleophilic functional groups attached to the same carbon atom and examples include amidines, amides, thioamides and 2-aminopyridines (Figure 4.4). They would be expected to yield [5,6]-ring fused systems on reaction with tetrafluoropyridazine.

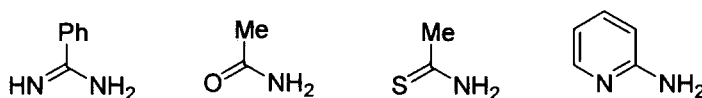
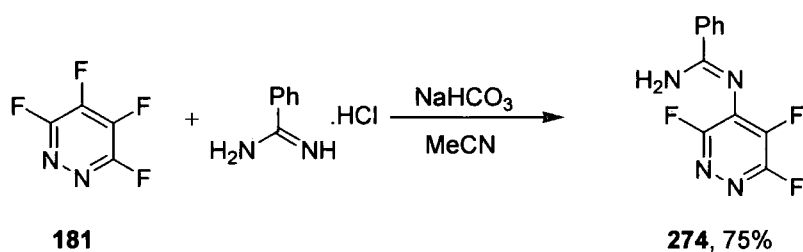


Figure 4.4

4.4.1 Reactions of Tetrafluoropyridazine with Amidine and Thioamide Derivatives

Reaction of tetrafluoropyridazine with amidine dinucleophiles should yield [5,6]-ring fused imidazopyridazine scaffolds that are potentially biologically interesting as pyridazine analogues of purines.

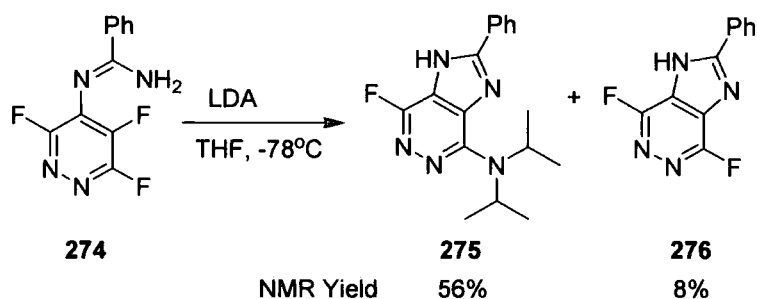
Reaction of tetrafluoropyridazine with benzamidine hydrochloride in acetonitrile at reflux temperature in the presence of four equivalents of sodium bicarbonate yielded the 4-substituted uncyclised amidine derivative **274** (Scheme 4.17).



Scheme 4.17

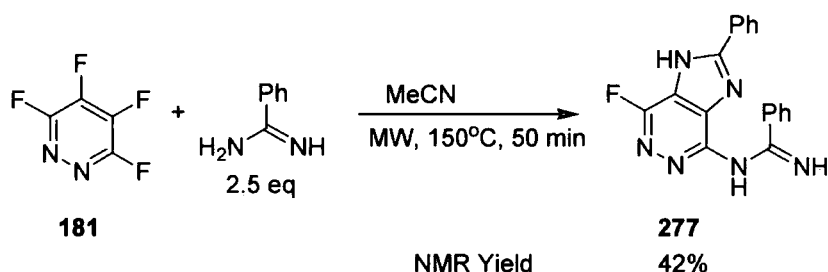
It was thought that treatment of this uncyclised amidine with strong, non-nucleophilic base should allow for the synthesis of the cyclic derivative *via* a more nucleophilic deprotonated intermediate. A range of bases were reacted with the uncyclised amidine at 0°C in an attempt to effect the desired cyclisation. Reactions were performed on a 0.1g scale and were monitored by ^{19}F NMR. *n*-BuLi and LiHMDS gave a complex product mixture, whilst LDA resulted in the formation of two new products.

The reaction with LDA was scaled up in an attempt to allow product isolation and identification (Scheme 4.18). The desired cyclic scaffold **276** was observed in small quantities by GC-MS and ^{19}F NMR, however, the reaction mixture was moderately complex. No products could be obtained cleanly, but NMR and GC-MS analysis suggested that the major component of the reaction mixture **275** had undergone nucleophilic attack by diisopropylamine as well as the desired cyclisation. It is not clear as to whether this nucleophilic attack occurred before or after cyclisation.



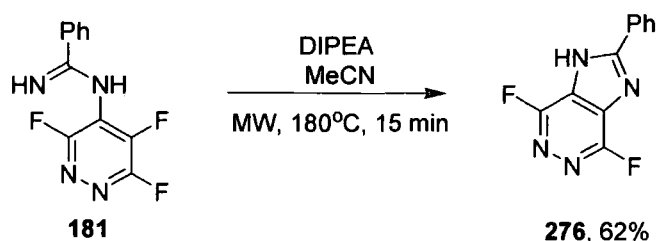
Scheme 4.18

Furthermore, tetrafluoropyridazine was reacted with excess (2.5eq) benzamidine under microwave irradiation at 150°C for 50 minutes. This gave a complex reaction mixture from which products could not be isolated, but GC-MS suggested that the major component of the reaction mixture was a cyclic derivative **277** that had again undergone nucleophilic attack by a second equivalent of benzamidine.



Scheme 4.19

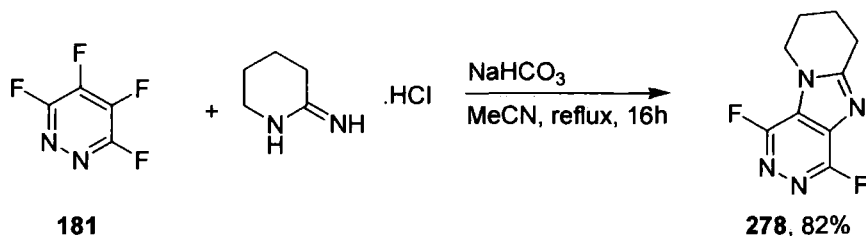
Therefore, a base of even lower nucleophilicity than diisopropylamine was required to allow the reaction to proceed without further nucleophilic attack. Hünig's base (diisopropylethylamine) was chosen because of its extreme steric demand, although its pK_a (11.4) is unlikely to be sufficiently basic to allow deprotonation of the amidine, so microwave irradiation conditions were employed in an attempt to effect the cyclisation. Indeed, the desired cyclic derivative **276** was obtained in good yield after irradiation at 180°C for 15 minutes (Scheme 4.20).



Scheme 4.20

The product **276** was identified as an isomer cyclised between the 4- and 5-positions by the symmetry observed by NMR, due to tautomerism rendering both imidazole-type nitrogens equivalent. The ^{19}F NMR signal was at -89 ppm, characteristic of fluorine *ortho* to deshielding ring nitrogen.

The reaction of tetrafluoropyridazine with the cyclic amidine dinucleophile 2-iminopiperidine yielded the tricyclic scaffold **278** at reflux in acetonitrile (Scheme 4.21). In this case no uncyclised amidine derivative was observed and the reaction proceeded under milder conditions than those observed with benzamidine due to the enhanced nucleophilicity of the cyclic system.

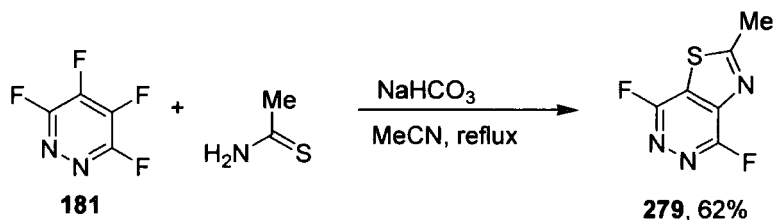


Scheme 4.21

This derivative displayed two separate ^{19}F NMR resonances as this is a non-symmetrical system and the chemical shifts observed (-93 and -95 ppm) were both characteristic of fluorine *ortho* to ring nitrogen. It is not possible in this case to determine whether the piperidine or imine-like nitrogen attacked the pyridazine ring first due to the symmetry of the pyridazine ring system but related reactions involving pentafluoropyridazine showed initial nucleophilic attack to occur through the piperidine ring nitrogen¹⁵⁸.

Reaction of tetrafluoropyridazine with thioacetamide proceeded to give the cyclic derivative **279** in a single step at reflux in acetonitrile in the presence of sodium hydrogen

carbonate (Scheme 4.22). Milder conditions were required than for amidines due to the increased nucleophilicity of sulfur relative to nitrogen.



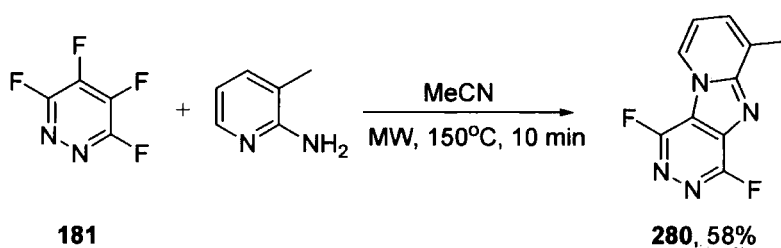
Scheme 4.22

Interestingly, compound **279** displayed unusual equivalences in its NMR spectra, showing a single ^{19}F NMR resonance at -82 ppm and two ^{13}C signals representing the four pyridazine ring carbons, suggesting that replacement of NH by S has a minimal influence on the NMR properties of the system and that this gives a spectrum that appears to be derived from a symmetrical system.

4.4.2 Reaction of Tetrafluoropyridazine with 2-Aminopyridine Derivatives

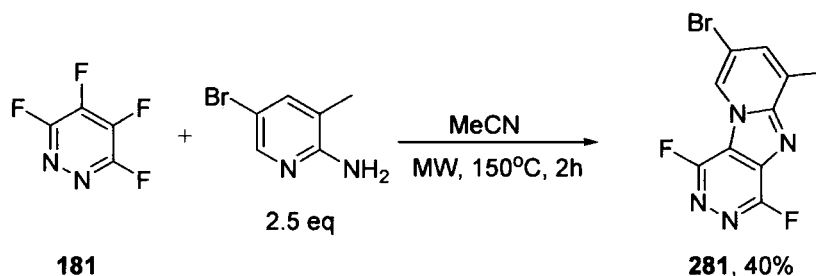
2-Aminopyridine derivatives possess an analogous 1,1-dinucleophile relationship to amidine derivatives and could be expected to form [5,6]-ring fused systems in a similar way.

Indeed, reaction of tetrafluoropyridazine with 2-aminopicoline under microwave irradiation in acetonitrile yielded a novel tricyclic aromatic ring system **280**, cyclised between the 4- and 5-positions (Scheme 4.23). Product identity and regiochemistry were again determined by ^{19}F NMR, displaying resonances at -90 and -92 ppm, characteristic of fluorine deshielded by *ortho* ring nitrogen.



Scheme 4.23

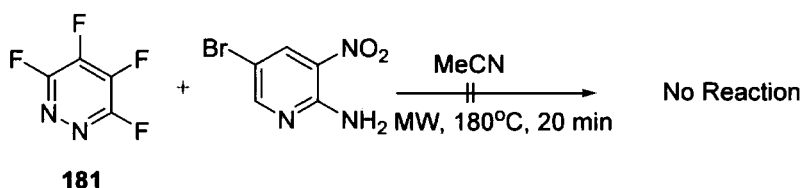
The analogous reaction of tetrafluoropyridazine and 2-amino-5-bromo-3-picoline yielded the corresponding tricyclic derivative **281** (Scheme 4.24), but the electron withdrawing effect of the bromine had a significant effect on reactivity by reducing the nucleophilicity of the pyridine and a longer reaction time of 2 hours, compared to ten minutes in the absence of bromine, was required.



Scheme 4.24

Monitoring of this reaction by ^{19}F NMR at regular intervals showed the steady consumption of starting material and formation of the cyclised product, with no evidence of any intermediate uncyclised products. This suggested that the rate determining step of this reaction was the initial nucleophilic attack of the aminopyridine and this was followed by a rapid cyclisation step. It is not possible in this case to determine whether the amino group or pyridine ring nitrogen attacked the pyridazine ring first due to the symmetry of the pyridazine system, however the site of initial attack in pentafluoropyridine has been shown to be the pyridine ring nitrogen¹⁵⁸.

Introduction of further electron withdrawing groups onto an aminopyridine reduced nucleophilicity to levels where reaction did not proceed. For example, 2-amino-5-bromo-3-nitropyridine was unreactive towards tetrafluoropyridazine (Scheme 4.25), and starting material was returned, even after microwave irradiation at 180°C for 20 minutes.



Scheme 4.25

A Scifinder and Beilstein search (performed on 22/10/08) on this tricyclic tetraazafluorene ring system showed that only three examples of this heteroaromatic substructure have been reported in the literature¹⁰⁰, ensuring that this is a potentially interesting scaffold for the synthesis of functionalised derivatives.

It was observed that solutions of these tricyclic derivatives were highly fluorescent in UV light and so absorption and fluorescence UV spectra of **280** were measured (Figure 4.5). Fluorescence spectroscopy gave the emission maximum at 360 nm, which is in the UV region of the electromagnetic spectrum, however a significant shoulder on this emission peak stretched into the blue visible region of the spectrum at around 400 nm, leading to the blue appearance of the samples under UV light. This fluorescence is likely to be due to the conjugated nature of this extended aromatic system.

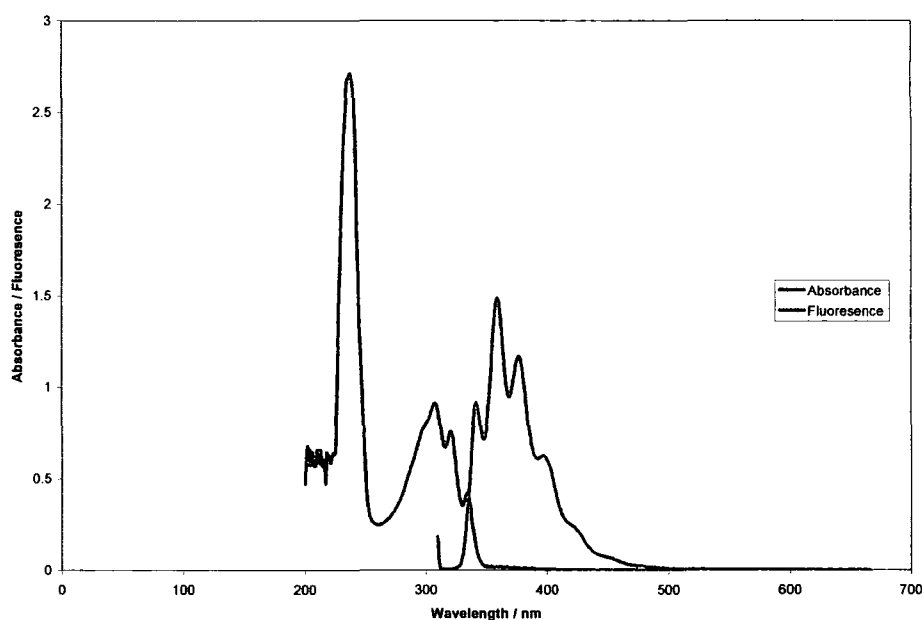


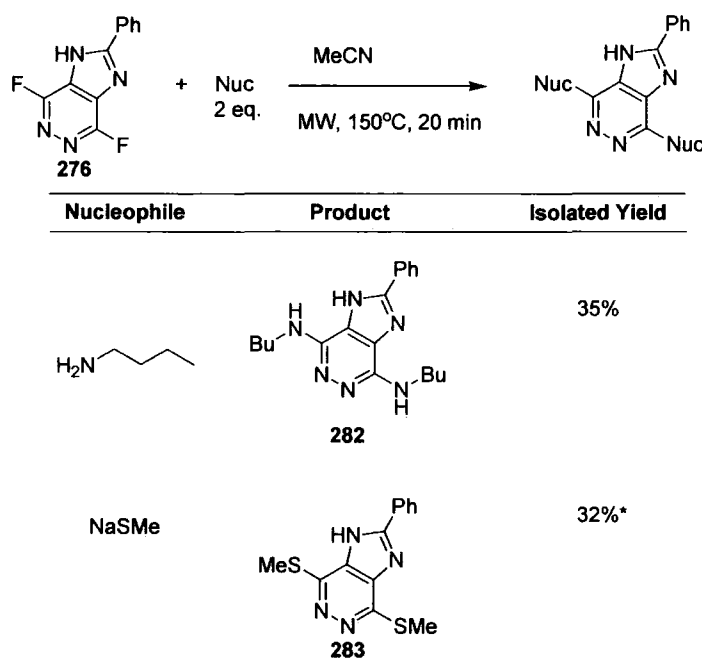
Figure 4.5: UV Absorption and fluorescence spectra of **280**

4.5 Functionalisation of [5,6]-Ring Fused Scaffolds

Again, all the [5,6]-ring fused scaffolds produced possess remaining ring fluorine atoms which may be susceptible towards nucleophilic displacement to obtain systems with a diverse range of functionality, as models for library synthesis of analogues.

4.5.1 Functionalisation of 1*H*-Imidazo[4,5-*d*]pyridazine Systems

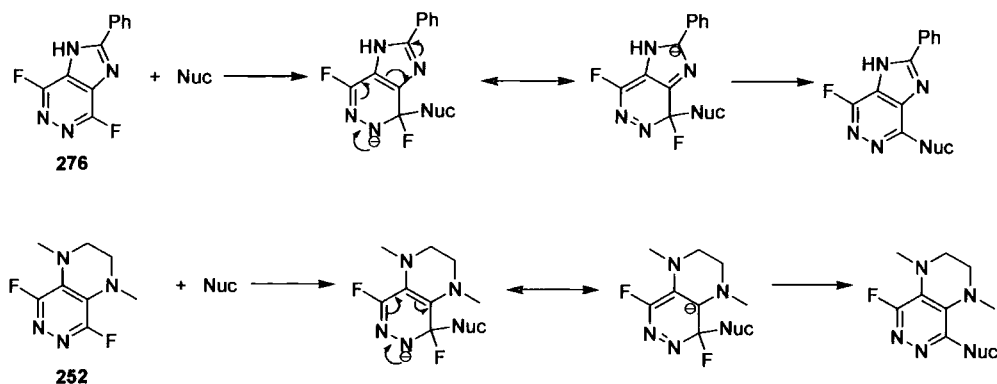
Reaction of 4,7-difluoro-2-phenyl-1*H*-imidazo[4,5-*d*]pyridazine **276** with two equivalents of the nucleophiles *n*-butylamine and sodium methanethiolate (Table 4.2) yielded the corresponding disubstituted systems resulting from replacement of both remaining ring fluorine atoms. In the case of *n*-butylamine this required the second equivalent to act as a nucleophile, as opposed to a base to neutralise the HF formed as a by-product in the reaction.



* Yield Reported with unidentified impurities

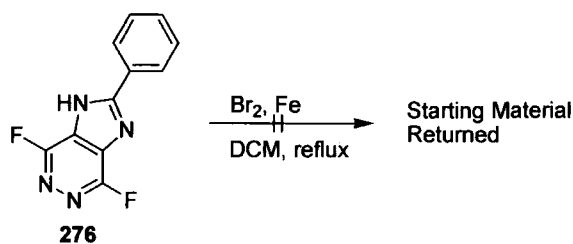
Table 4.2

These results highlight the increased reactivity of these [5,6]-ring fused systems relative to the [6,6]-fused systems described in the earlier part of this chapter. This is because in the [6,6]-fused systems the nitrogen substituents are effectively two deactivating amine groups, whereas in the above [5,6]-imidazo-pyridazine the extra conjugation provided by the additional aromatic ring provides extra stabilisation to the negative charge that develops in the Meisenheimer intermediate on substitution (Scheme 4.26).



Scheme 4.26

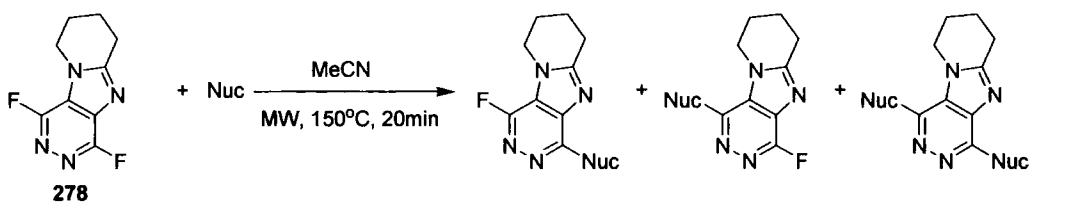
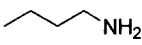
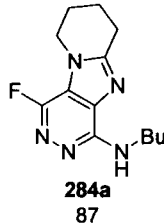
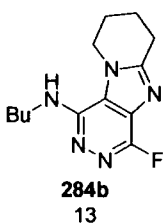
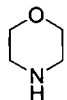
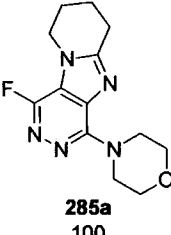
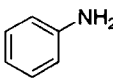
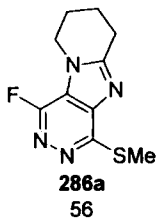
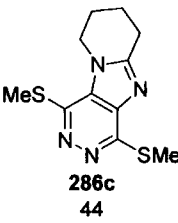
Halogenation of the pendant phenyl ring attached to the heteroaromatic system would provide an additional diversity point for functionalisation. However, attempted bromination of the phenyl ring using elemental bromine and an iron catalyst in refluxing dichloromethane returned only the starting material (Scheme 4.27). It is likely that the attachment of a nitrogen rich heterocycle to the phenyl ring is sufficiently electron withdrawing to deactivate the system towards electrophilic substitution and render it unreactive under the conditions examined.



Scheme 4.27

Similarly, the tricyclic ring fused scaffold **278** formed from reaction of tetrafluoropyridazine with the cyclic amidine 2-iminopiperidine reacts with nucleophiles under similar microwave irradiation conditions (Table 4.3). Reaction of scaffold **278** with morpholine and butylamine led to regioselective substitution, forming a single regioisomer in the case of morpholine. With the reactive sulfur nucleophile, sodium methanethiolate, a single monosubstituted product resulted, however a significant amount of disubstituted product was formed, resulting from replacement of both ring fluorine atoms, which was not separable from the monosubstituted isomer by chromatography. The aromatic amine

nucleophile, aniline, was not sufficiently nucleophilic to effect the displacement reaction, and unsubstituted starting material was returned, even after extended microwave irradiation.

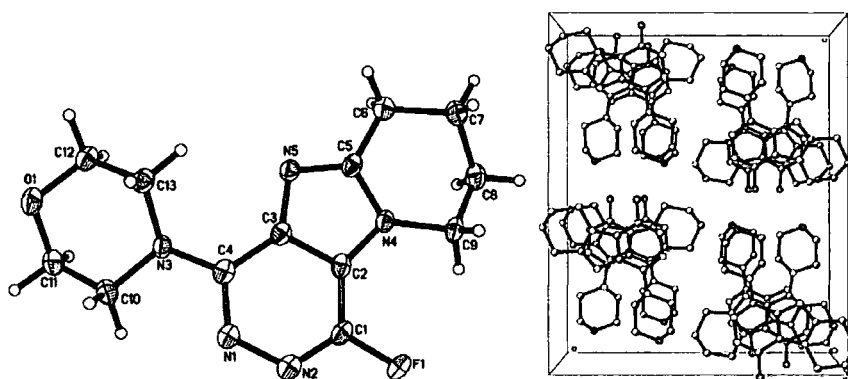
				
Nucleophile	Isolated Yield 1- Substituted Product	Ratio 1- Substituted Product	Ratio 4- Substituted Product	Ratio Disubstituted Product
	56*	 284a 87	 284b 13	-
	72	 285a 100	-	-
	No Reaction	-	-	-
NaSMe	Not Isolated	 286a 56	-	 286c 44

* Isolated as mixture of 1- and 4- monosubstituted regioisomers

Table 4.3

The major isomer of the morpholino derivative **285a** was shown to be substituted at the 1-position by X-ray crystallography (Figure 4.6), because definitive product

identification was extremely difficult by NMR. In the unit cell, a complex alternating arrangement of the tricyclic rings was observed that was held together by π -stacking and dipolar interactions.

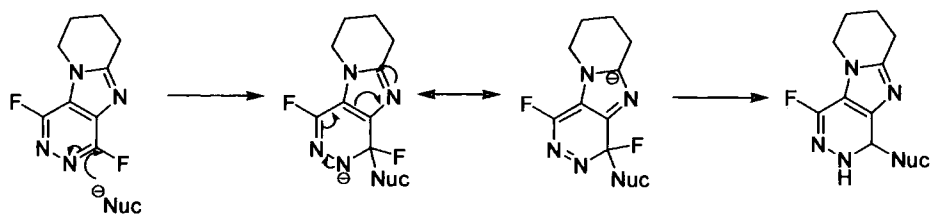


Bond	Bond Length / Å	Bond	Bond Length / Å
N(1)-C(4)	1.337	C(9)-C(8)	1.520
N(1)-N(2)	1.376	C(8)-C(7)	1.523
N(2)-C(1)	1.292	C(6)-C(7)	1.531
C(1)-C(2)	1.395	C(6)-N(5)	1.492
N(4)-C(2)	1.372	N(5)-C(5)	1.323
N(4)-C(9)	1.477	N(5)-C(3)	1.383
		C(3)-C(4)	1.428

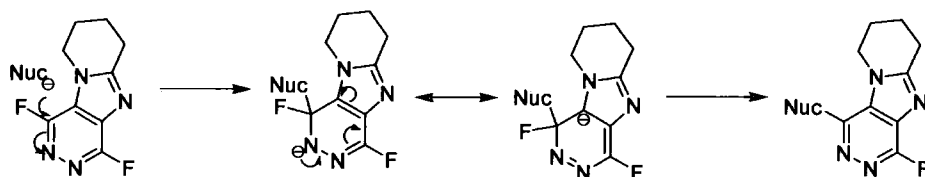
Figure 4.6: X-ray Crystal Structure of 4-fluoro-1-morpholin-4-yl-5,6,7,8-tetrahydro-2,3,4b,9-tetraaza-fluorene **285a**

Attack at this site allows delocalisation of the negative charge formed in the Meisenheimer intermediate around the whole imidazopyridazine ring system, whilst attack at C4 allows delocalisation only around the pyridazine ring (Scheme 4.28). Although crystal structures of the other derivatives could not be obtained, the similarity of their respective NMR spectra to this derivative would suggest that they too are substituted at the 1-position.

Attack at C1

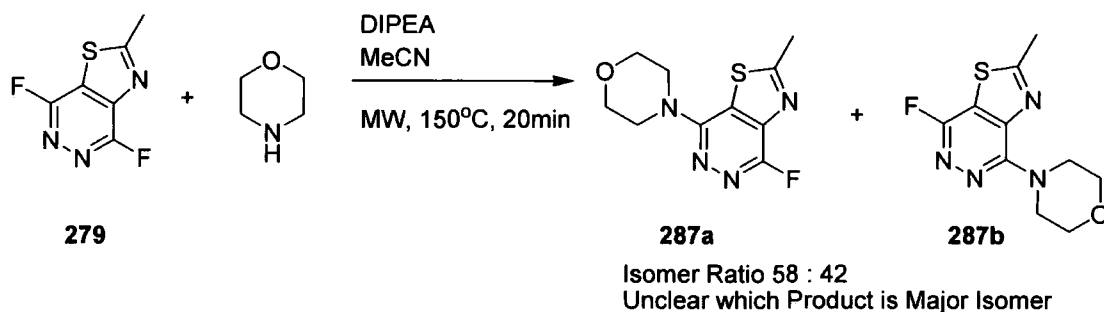


Attack at C4



Scheme 4.28

Substitution of the thiazolopyridazine scaffold **279** was achieved successfully using morpholine as nucleophile (Scheme 4.29), but it is not clear without crystallography whether this compound underwent substitution adjacent to sulfur or nitrogen and, unfortunately, crystals suitable for X-ray diffraction could not be obtained. Isolated yields of both products were moderate due to significant formation of tarry by products and the use of several other nucleophiles including butylamine, sodium methanethiolate and aniline under identical conditions led to total decomposition of the starting material.



Scheme 4.29

4.5.2 Functionalisation of Tetraazafluorene Scaffolds

Non-symmetrical tetraazafluorene scaffolds have the potential to give regioisomeric nucleophilic monosubstitution products by displacement of either fluorine atom. 1,4-Difluoro-8-methyl-2,3,4*b*,9-tetraaza-fluorene **280** reacts with nucleophiles under microwave irradiation in acetonitrile (Table 4.4) to give both substituted isomers, however

substitution is favoured at the 1-position, being almost exclusive in the case of diethylamine. In each case only the major isomer was isolated as a pure sample by chromatography or recrystallisation and characterised spectroscopically.

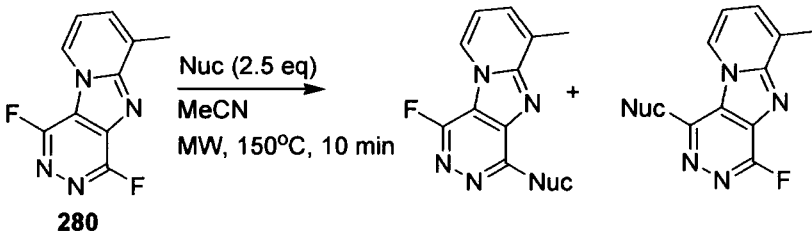
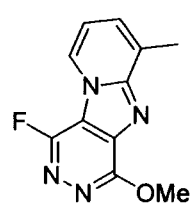
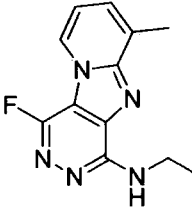
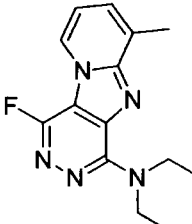
 <p style="text-align: center;">280</p>		
Nucleophile	Isolated Product	Isomer Ratio
NaOMe	 <p style="text-align: center;">288, 40%</p>	76 : 24
NH ₂ Et	 <p style="text-align: center;">289, 65%</p>	79 : 21
NHEt ₂	 <p style="text-align: center;">290, 70%</p>	95 : 5

Table 4.4

The two possible regioisomers obtained from monosubstitution on this scaffold are difficult to distinguish by a simple consideration of their NMR spectra. X-ray

crystallography of the 1-diethylamino derivative **290** proved the structure of this compound (Figure 4.7), and the similarity of the NMR data of the other two derivatives to the known structure would suggest that they too are substituted at the 1-position.

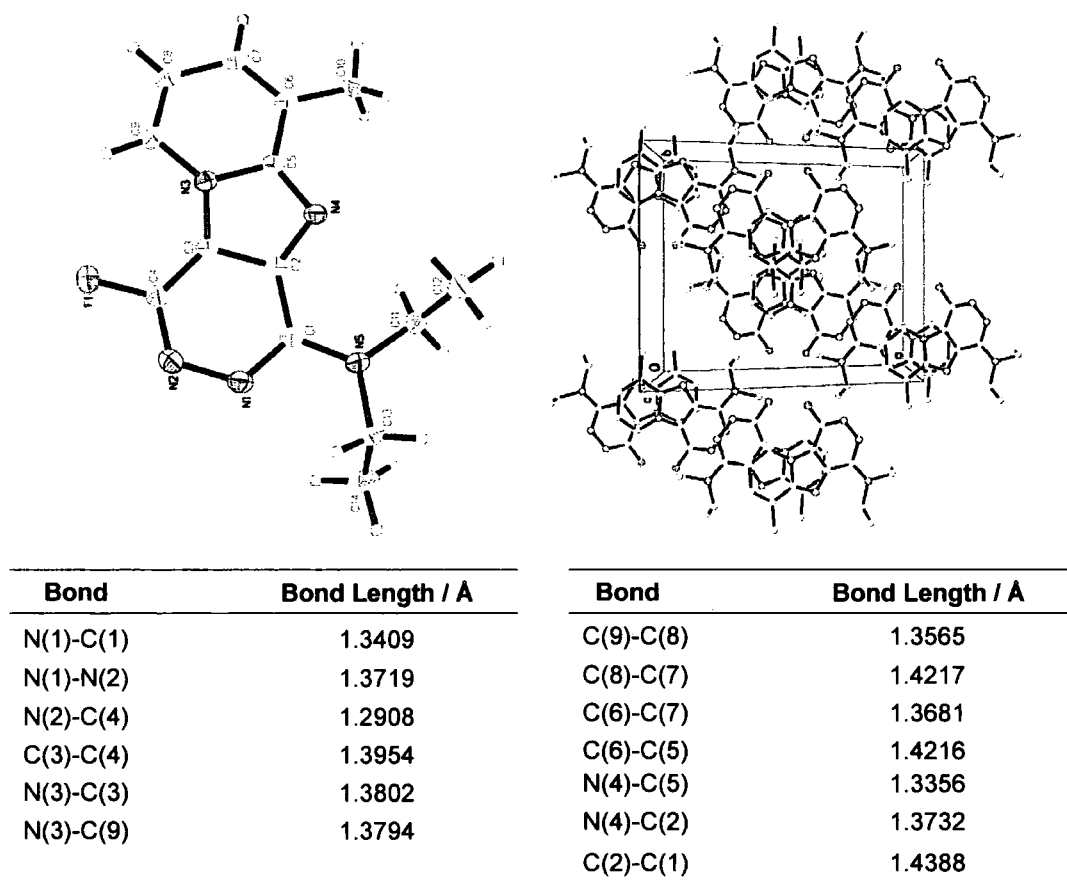
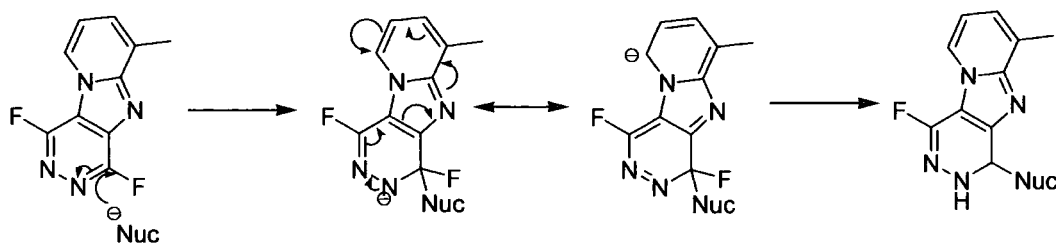
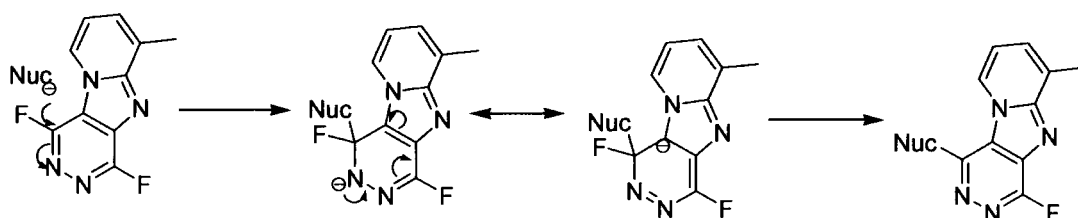


Figure 4.7: X-Ray Crystal Structure of Diethyl-(4-fluoro-8-methyl-2,3,4b,9-tetraazafluoren-1-yl)-amine **290**

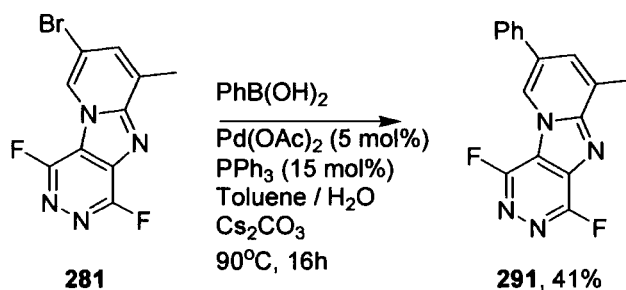
This regioselectivity can be explained by a consideration of the mechanism of this process. Attack at C1 allows the negative charge in the Meisenheimer intermediate to be delocalised around the whole tricyclic aromatic system, whilst attack at C4 allows charge to be delocalised only around the pyridazine ring (Scheme 4.30). The reaction therefore proceeds *via* the most stabilised (delocalised) Meisenheimer intermediate.

Attack at C1**Attack at C4**

Scheme 4.30

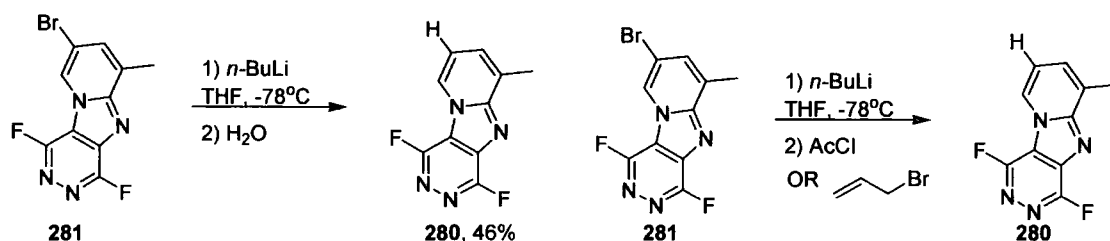
Attempts were then carried out to functionalise the tricyclic tetraazafluorene scaffolds using chemistry other than nucleophilic aromatic substitution. In particular, the bromine atom present in scaffold **281** could potentially be used for palladium catalysed cross-coupling reactions, or for debromo-metallation processes and trapping with an electrophile.

Suzuki-Miyaura coupling of **281** with phenyl boronic acid proceeded in moderate yield under reflux in a biphasic mixture of toluene and water (Scheme 4.31). Conditions were not optimised and this may improve the yield as cross-coupling processes are known to be highly sensitive to factors such as catalyst, ligand, solvent and base.



Scheme 4.31

Attempts were carried out to utilise lithium-halogen exchange at the bromine atom of scaffold **281**, followed by attempted trapping with H^+ , allyl bromide and acetyl chloride under rigorously anhydrous conditions. In the case of H^+ as electrophile successful trapping was observed, however the use of the alkyl electrophiles also formed this hydro-product. As conditions were anhydrous, it is likely that the lithio derivative formed is a highly stabilised anion and this ensures that the trapping process is very slow, and does not proceed until the reaction is quenched using a large excess of water.



Scheme 4.32

4.6 Conclusion

A range of ring fused systems have been synthesised by reaction of tetrafluoropyridazine with dinucleophiles. Many of the ring fused heterocycles synthesised here have seen little attention previously due to difficulties in their syntheses using standard methodologies. Reaction with 1,2-dinucleophiles such as diamines, diols and dithiols yields [6,6]-ring fused systems, whilst the use of 1,1-dinucleophiles such as amidines, thioamides and 2-aminopyridines afford [5,6]-ring fused systems. A selection of the scaffold frameworks synthesised are shown along with the number of Scifinder ‘hits’ for each parent scaffold in Figure 4.8. This shows the scarcity of the majority of the scaffolds developed with only significant numbers of analogues of the imidazopyridazine and thiazolopyridazine scaffolds synthesised.

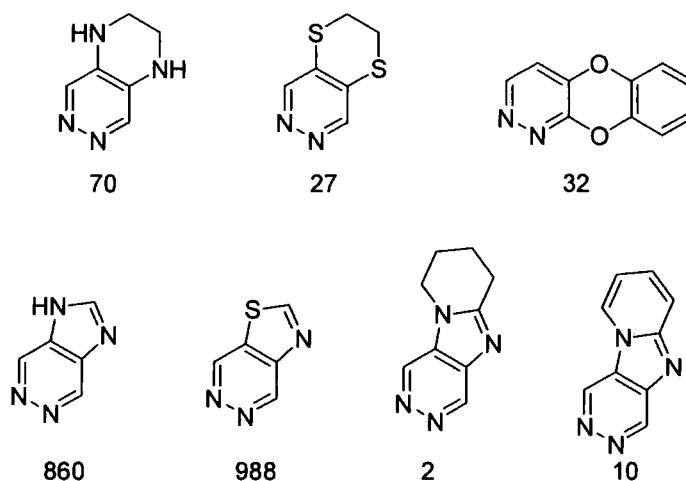


Figure 4.8: Scifinder 'hits' for Scaffolds Synthesised (Accessed 1/12/08)

The ring fused scaffolds produced have fluorine atoms which can be displaced in further substitution reactions, which often proceed with a high degree of regiocontrol. This strategy has yielded a range of fused pyridazine derivatives with moderate skeletal and substituent diversity.

Chapter 5

Chemistry of Tetrachloropyridazine

5.1 Introduction

Tetrachloropyridazine **292** is also susceptible towards nucleophilic displacement chemistry, but the decreased strength of the C-Cl bond relative to the C-F bond means that tetrachloropyridazine could, potentially, offer other synthetic possibilities compared to tetrafluoropyridazine in cross-coupling and metallation processes (Figure 5.1).

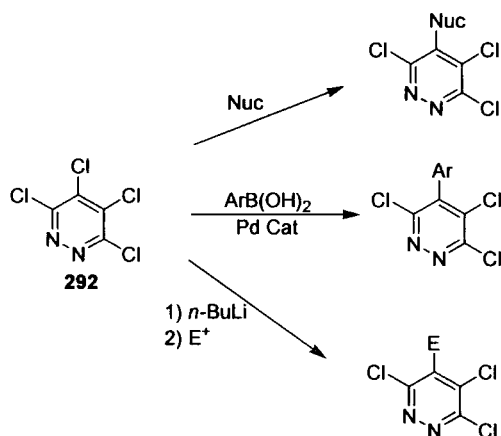


Figure 5.1

The palladium catalysed cross-coupling of chlorinated aromatic systems was initially seen as a difficult synthetic problem, but the development of new ligands and conditions has now reached the stage where such reactions are now feasible. Indeed, for many systems cross-coupling can be successfully achieved using standard catalysts, such as $\text{Pd}(\text{PPh}_3)_4$. However, to date, very few examples of palladium catalysed reactions of perchlorinated heteroaromatics have been reported in the literature.

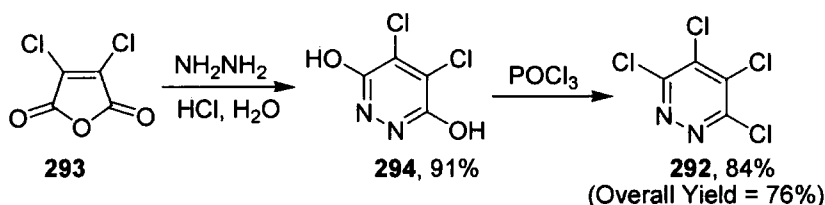
Dechloro-metallation of perchloroheteroaromatic systems is another potentially useful process as this will allow reaction with electrophilic species, which are typically unreactive towards electron-poor pyridazine derivatives. Generally, metal-halogen exchange is observed in brominated systems and is extremely difficult in chlorinated systems, however, both lithiation and magnesiation processes have been observed in

perchlorinated heteroaromatic derivatives, such as pentachloropyridine¹⁵⁹. However, the corresponding chemistry has not been explored using tetrachloropyridazine as the substrate.

The difficulty in characterising highly chlorinated systems has hampered the development of the chemistry of perchlorinated systems because of the lack of effective structural probes for NMR. ¹³C NMR may offer some potential in assigning product structures, but, to date, it has proved difficult to correlate experimental and calculated chemical shifts. Therefore, it is likely that X-ray crystallography, which today is a rapid and highly informative technique, may be most appropriate in deducing product identity.

5.2 Synthesis of Tetrachloropyridazine

Tetrachloropyridazine **292** can be synthesised in good yield in a two step process starting from dichloromaleic anhydride **293** (Scheme 5.1). Firstly, ring expansion of dichloromaleic anhydride with hydrazine hydrate yields 4,5-dichloro-3,6-dihydroxypyridazine **294**, which is followed by chlorination with phosphorus(V) oxychloride to produce tetrachloropyridazine, in 76% overall yield based on the mass of dichloromaleic anhydride used. This process was applicable to large scale chemistry, being carried out in 100g batches. However, on such a large scale safety precautions must be taken on quenching the phosphorus(V) oxychloride, which is highly exothermic.



Scheme 5.1

5.3 Nucleophilic Aromatic Substitution Reactions of Tetrachloropyridazine

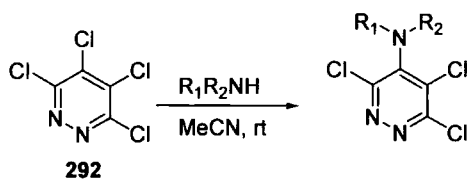
5.3.1 Monosubstitution

A single example of nucleophilic substitution involving tetrachloropyridazine as the electrophile has been previously reported, namely reaction with dimethylformamide, which has been claimed to provide the 3-dimethylamino derivative in good yield (Scheme 5.2)¹⁶⁰.



Scheme 5.2

It was decided to examine the regioselectivity of attack of various amine nucleophiles on tetrachloropyridazine, achieved by stirring two equivalents of amine with tetrachloropyridazine at room temperature in acetonitrile. Reaction of a broad selection of primary and secondary aliphatic amines resulted in the regioselective formation of a single monosubstituted isomer (Table 5.1). Consumption of starting material was 100% as observed by TLC and GC analysis and purities of products obtained were good; analytically pure material was obtained in moderate yield by a single recrystallisation.



$\text{R}_1\text{R}_2\text{NH}$	Product	Isolated Yield	$\text{R}_1\text{R}_2\text{NH}$	Product	Isolated Yield
<chem>CH3NH2</chem>	 296	43%		 299	49%
	 297	54%		 300	25%
	 298	45%		 301	47%

Table 5.1

Structural determination by X-ray crystallography of the benzylamino **297** and diethylamino **299** derivatives confirmed that substitution had occurred at the 4-position, *para* to activating ring nitrogen (Figure 5.2).

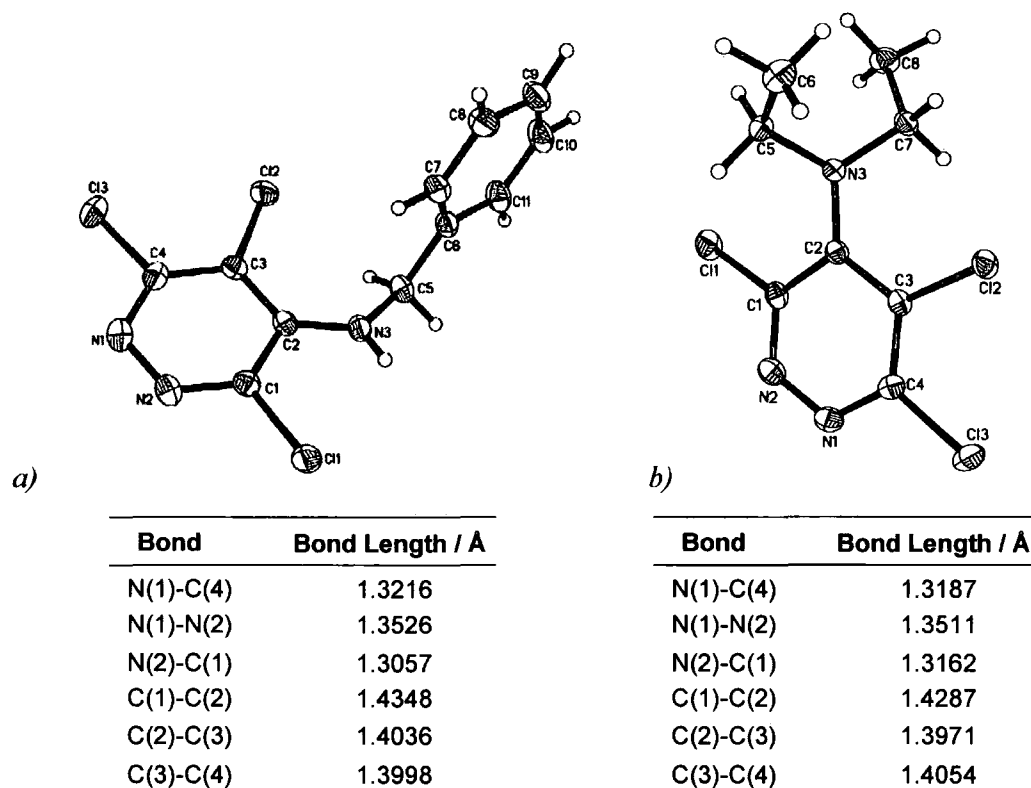
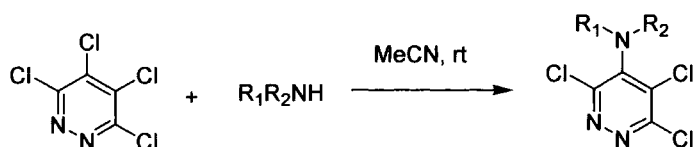


Figure 5.2: X-ray Crystal Structures of a) *N*-benzyl-3,5,6-trichloropyridazin-4-amine **297** and b) 3,5,6-trichloro-*N,N*-diethylpyridazin-4-amine **299**

Comparison of ^{13}C NMR chemical shifts of the primary amine substituted products to the benzylamino derivative and secondary amine substituted products to the diethylamino derivative would suggest that substitution has occurred at C4 in all cases (Table 5.2).



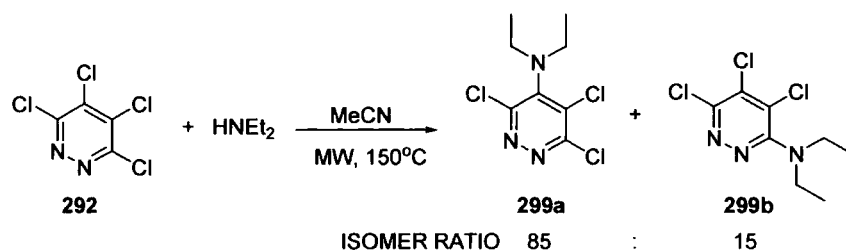
R ₁	R ₂	δ_{C5} / ppm	δ_{C4} / ppm	δ_{C6} / ppm	δ_{C3} / ppm
Bn	H	116.8	141.4	144.1	154.8
Me	H	115.8	142.1	143.6	154.8
<i>t</i> -Bu	H	121.7	142.9	148.4	155.0
Et	Et	133.2	146.4	155.1	155.4
Piperidino		129.7	146.8	152.8	155.5
Morpholino		130.3	145.5	152.7	155.7

Table 5.2

Such highly regioselective reactions are quite unusual in the reactions of perchloroheteroaromatics, since, for example pentachloropyridine reacts with nucleophiles to give mixtures of regioisomeric products substituted at the 4- and 2-positions, which is thought to be due to competing substitution at the less sterically hindered 2-position. In the case of tetrachloropyridazine, the additional activation provided by the second ring nitrogen must outweigh any steric preference for reaction at the less hindered site.

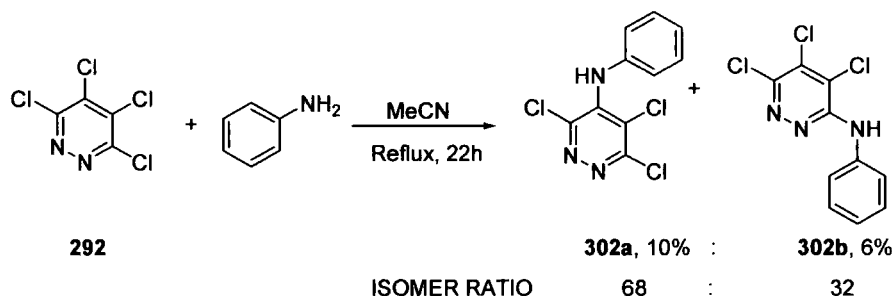
The observed regioselectivity is in disagreement with the findings of Lee *et al.*¹⁶⁰ who suggested that reaction of tetrachloropyridazine in refluxing DMF, which results in the formation of dimethylamine by thermal decomposition, proceeds exclusively at the 3-position, the opposite isomer to that observed in this study. It is likely that in the harsher conditions used in their experiment, thermodynamic control resulted in the formation of the less sterically hindered isomer. However, at room temperature kinetic control results in reaction at the most activated site *para* to ring nitrogen.

Repetition of the reaction of tetrachloropyridazine with diethylamine under microwave irradiation at 150°C in acetonitrile resulted in the formation of both 4- and 3-monosubstituted isomers in a ratio of 85 : 15 respectively (Scheme 5.3), demonstrating that some of the thermodynamic product is formed under more forcing conditions, although it is not the major product. Product identity was assigned by comparison of spectral data to the pure sample obtained at room temperature.

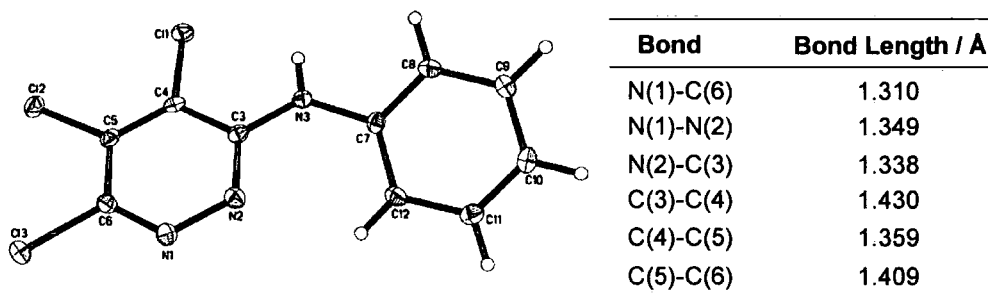


Scheme 5.3

A less nucleophilic aromatic amine nucleophile, aniline, did not react with tetrachloropyridazine at room temperature, so elevated temperatures were employed to effect the substitution. In refluxing acetonitrile 4- and 3-monosubstituted isomers were produced in a 68 : 32 ratio respectively by integration of the crude ^1H NMR spectrum, and conversion and purity was high (Scheme 5.4). However, separation of the two regioisomers was difficult, as they co-eluted on column chromatography leading to very low isolated yields, although analytically pure samples of both isomers were obtained. A crystal structure of the minor isomer confirmed it to be substituted at the 3-position, confirming that the major product was the 4-substituted isomer (Figure 5.3).



Scheme 5.4

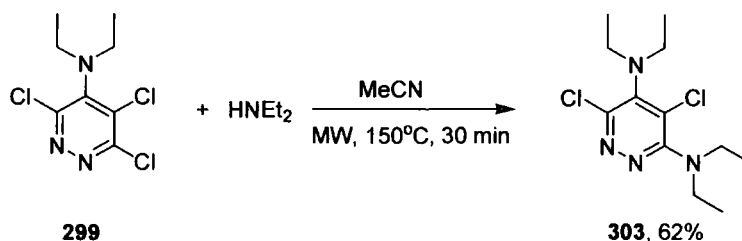
Figure 5.3: X-ray Crystal Structure of 4,5,6-trichloro-N-phenylpyridazin-3-amine **302b**

5.3.2 Disubstitution

For tetrachloropyridazine to be a good scaffold for sequential nucleophilic substitution reactions a second substitution step should also proceed efficiently and with high regioselectivity.

The second substitution step did not proceed at room temperature or in refluxing acetonitrile, for example, reaction of 4-benzylamino-3,5,6-trichloropyridazine **297** with a second equivalent of benzylamine, or reaction of 4-diethylamino-3,5,6-trichloropyridazine **299** with a second equivalent of diethylamine at reflux returned only the starting materials.

Under microwave irradiation conditions, disubstitution reactions began to become feasible. For example, 4-diethylamino-3,5,6-trichloropyridazine **299** reacted with a second equivalent of diethylamine with a high degree of regiocontrol (Scheme 5.5). The major product **303** was unsymmetrically substituted as it displayed two sets of signals for the CH₂ and CH₃ groups in its ¹H and ¹³C NMR spectra. NOESY correlation spectroscopy would suggest that the product is 4,6-disubstituted, rather than 5,6-disubstituted because no cross signals between the two alkyl groups are observed.



Scheme 5.5

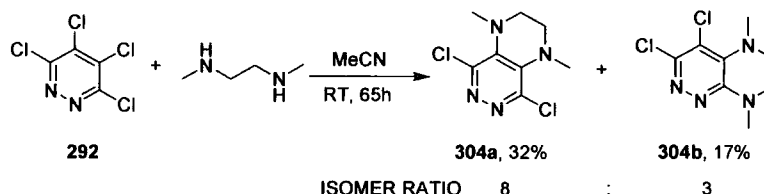
However, when 4-diethylamino-3,5,6-trichloropyridazine was reacted with sodium methoxide a complex mixture of all three possible disubstituted isomers was obtained in a ratio of 50 : 33 : 17 and as separation of these regioisomers was not possible by chromatography it is not possible to assign a structure to any of these systems. It is likely that the decreased steric demand and increased nucleophilicity of sodium methoxide relative to diethylamine leads to this decrease in selectivity. Similarly, 4-benzylamino-3,5,6-trichloropyridazine reacts with a second equivalent of benzylamine to give an inseparable mixture of all three possible regioisomers in a ratio of 43 : 30 : 27.

Consequently, 4-amino-trichloropyridazine derivatives are deactivated towards sequential displacement reactions with nucleophiles. Forcing microwave irradiation conditions are required to achieve conversion, and regioselectivity can be low.

5.4 Ring Fused Systems from Tetrachloropyridazine

Tetrachloropyridazine has the potential to react with dinucleophilic species in an analogous fashion to tetrafluoropyridazine to provide ring fused pyridazine scaffolds. Tetrachloropyridazine was reacted with some of the dinucleophiles that led to successful annelation with tetrafluoropyridazine to compare the reactivity of the fluorinated and chlorinated systems.

Reaction of tetrachloropyridazine with *N,N'*-dimethylethylenediamine proceeded to give a mixture of cyclic products in a ratio of 8:3 on stirring at room temperature in acetonitrile (Scheme 5.6). The major product **304a** was shown to be cyclised between the 4- and 5-positions, both *para* to activating ring nitrogen, by the presence of single resonances in the ^1H and ^{13}C NMR spectra for the CH_2 and CH_3 signals, due to the symmetry of the system. The structure of the major product was also confirmed by X-ray crystallography (Figure 5.4).



Scheme 5.6

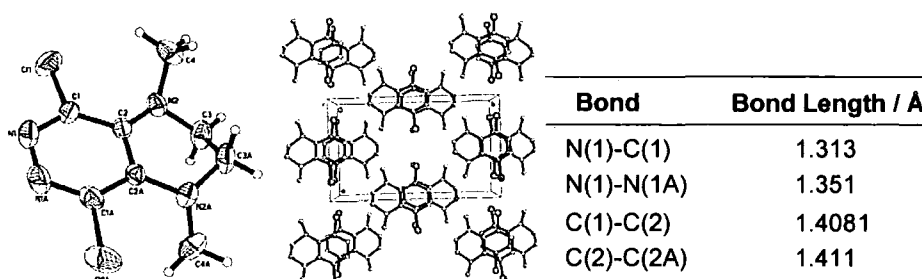
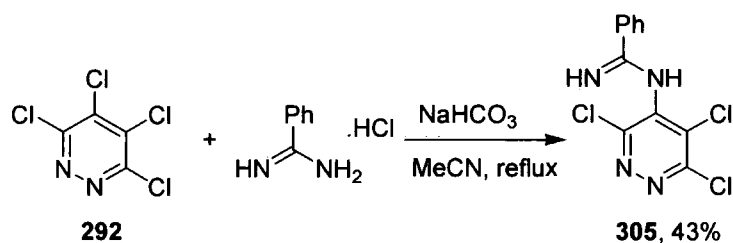


Figure 5.4: X-ray Crystal Structure of 5,8-dichloro-1,2,3,4-tetrahydro-1,4-dimethylpyrazino[2,3-*d*]pyridazine **304a**

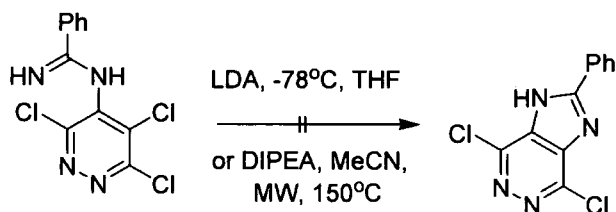
This result is in contrast to that obtained with tetrafluoropyridazine, which gave a single regioisomer, cyclised between the 4- and 5-positions, on reaction with N,N'-dimethylethylenediamine under identical conditions to those used here. This demonstrates the increased reactivity of the fluorinated system, which undergoes rapid annelation to give the kinetic product by reaction at both of the most reactive sites *para* to ring nitrogen. Also, the increased steric demand of the chlorinated system leads to some cyclisation at the less hindered 3-position, *ortho* to ring nitrogen, to give some of the thermodynamic product.

Similarly, the reaction of 1,1-dinucleophiles such as amidines could be expected to yield corresponding [5,6]-ring fused products. As was the case for tetrafluoropyridazine, reaction of tetrachloropyridazine with benzamidine hydrochloride yielded a monosubstituted uncyclised product **305** in refluxing acetonitrile (Scheme 5.7).



Scheme 5.7

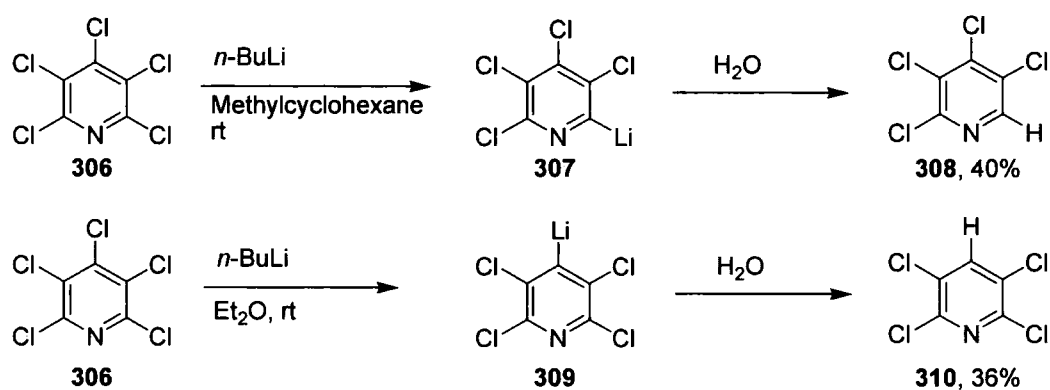
All attempts to induce the cyclisation proved unsuccessful (Scheme 5.8) including the use of strong bases such as LDA or NaH, or the microwave irradiation technique in the presence of Hünig's base which successfully effected the cyclisation of the polyfluorinated analogue. This demonstrates the decreased reactivity of polychlorinated heteroaromatics relative to polyfluorinated heteroaromatics in nucleophilic displacement processes.



Scheme 5.8

5.5 Metallation

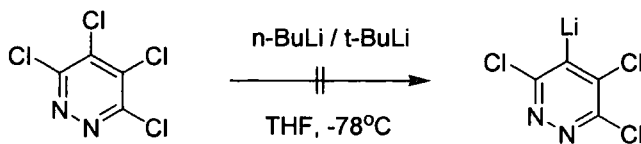
Although metal-halogen exchange reactions at C-Cl bonds are generally considered to be difficult, such reactions have been successfully accomplished using perchlorinated heteroaromatic substrates. For example, pentachloropyridine **306** has been shown to undergo lithiation reactions whose regiochemistry is solvent dependent (Scheme 5.9)¹⁶¹. In methylcyclohexane lithiation of pentachloropyridine occurs mainly at the 2-position, whilst in diethyl ether a 4-lithio derivative is formed.



Scheme 5.9

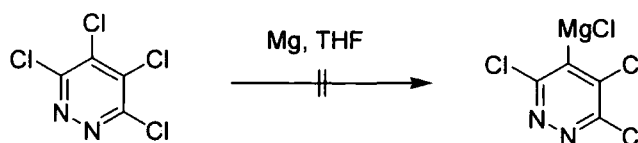
The potential to carry out metallation reactions on tetrachloropyridazine would be desirable, as this would allow the introduction of functionality that is complimentary to that which can be introduced using nucleophilic substitution reactions.

On addition of both *n*-BuLi and *t*-BuLi to a solution of tetrachloropyridazine in THF at -78°C a rapid darkening of the solution was observed and a complex product mixture was obtained after aqueous work-up (Scheme 5.10). ¹³C NMR and GC-MS showed the major component of the reaction mixture was starting material, however the significant number of by-products could not be identified.



Scheme 5.10

Attempted formation of a Grignard reagent from tetrachloropyridazine failed to initiate, even on heating of the reaction mixture, or on addition of initiators such as iodine or 1,2-dibromoethane (Scheme 5.11).



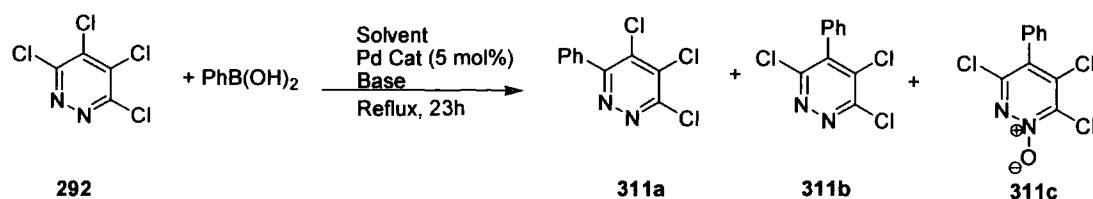
Scheme 5.11

It would therefore seem that, under the conditions examined, metallation of tetrachloropyridazine is very difficult and was not investigated further.

5.6 Palladium Catalysed Cross-Coupling Reactions

The cross-coupling of chloroheteroaromatics has been extensively examined in recent years and is now commonly used in the synthesis of C-C bonds. However, the study of perchlorinated heteroaromatic compounds as substrates in palladium catalysed cross-couplings has been limited to a single recent report on the regioselective Suzuki cross-coupling of tetrachloropyrimidine¹⁶². To date, the chemistry of tetrachloropyridazine in palladium catalysed cross-coupling processes has not been examined.

Cross-coupling reactions are typically sensitive to conditions such as solvent, catalyst and base used in the reaction. Therefore, a range of these potential factors were screened in small scale reactions of tetrachloropyridazine with phenyl boronic acid, and the results analysed by GC-MS, which are summarised in Table 5.3.



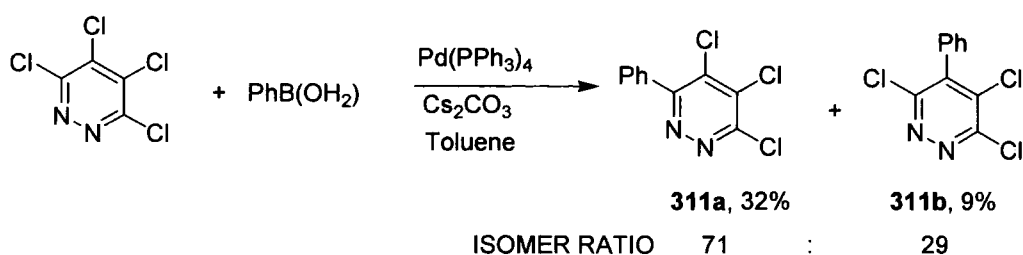
Reaction	Solvent	Pd Catalyst	Base	Conversion	Ratio 311 a:b:c
1	Toluene	Pd(PPh ₃) ₄	Cs ₂ CO ₃	72	75 : 15 : 8
2	THF	Pd(PPh ₃) ₄	Cs ₂ CO ₃	43	63 : 37 : 0
3	MeCN	Pd(PPh ₃) ₄	Cs ₂ CO ₃	13	56 : 30 : 14
4	DMF	Pd(PPh ₃) ₄	Cs ₂ CO ₃	0	-
5	Toluene	Pd(PPh ₃) ₄ ^a	Cs ₂ CO ₃	77	58 : 23 : 19
6	Toluene	Pd / C	Cs ₂ CO ₃	0	-
7	Toluene	Pd(PPh ₃) ₄	KF	62	69 : 18 : 13
8	Toluene	Pd(PPh ₃) ₄	KCl	0	-

^a 10 mol% catalyst used

Table 5.3

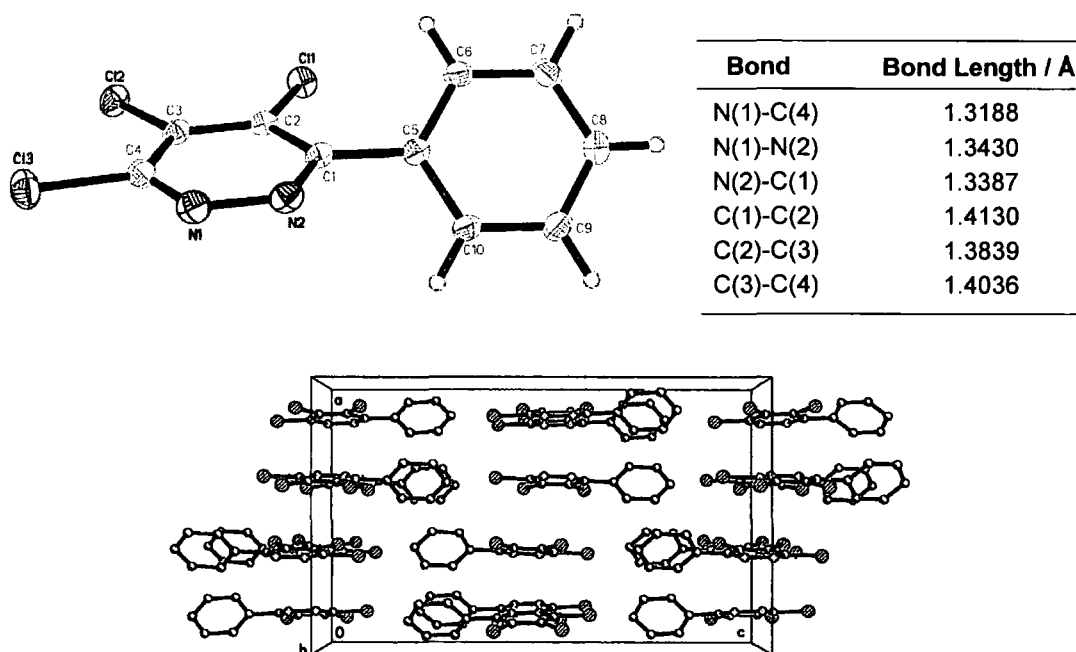
These results suggest that the best combination of solvent and base is toluene and CsCO₃. The increase in catalyst loading from 5 mol% to 10 mol% led to a slight increase in conversion, but a decrease in regioselectivity was also observed. Alternative ligands to PPh₃ were not screened in the reaction as it was hoped to develop a process using readily available starting materials.

Our optimised conditions were used in a larger scale cross-coupling reaction to allow product isolation and identification (Scheme 5.12). Some *N*-oxide by-product **311c** was also observed in the screening reactions, and is most likely formed due to incomplete deoxygenation of the reaction mixture by sparging with argon. Therefore a freeze-pump-thaw technique was employed in this larger scale reaction to ensure more rigorous solvent deoxygenation, which eliminated formation of this by-product. Isolated yields of both isomers was moderate due to difficult purification in both separation of the isomers and removal of the Ph₃P and Ph₃P=O by-products.



Scheme 5.12

X-ray crystallography of the major isomer **311a** showed it to be substituted at the 3-position (Figure 5.5), which is the opposite site of substitution to that obtained with nucleophilic attack. This is likely to be due to the reduced steric hindrance at this site as formation of the tetrasubstituted palladium intermediates obtained in the catalytic cycle is quite a sterically demanding process and proceeds most efficiently when the site of substitution does not have two *ortho*-substituents. The crystal structure shows the two rings to be almost orthogonal to each other and stacking of phenyl and pyridazine rings occurs in the unit cell.

Figure 5.5: X-ray Crystal Structure of 3,4,5-trichloro-6-phenylpyridazine **311a**

However, when this cross-coupling was repeated with a range of boronic acids, the results were substrate sensitive and unpredictable (Table 5.4). Substitution was successfully achieved using 4-methylbenzene boronic acid and (*E*)-2-phenylvinylboronic acid. In both cases purification was difficult and the reported yield is of product contaminated with some Ph_3P and $\text{Ph}_3\text{P}=\text{O}$. In the absence of a crystal structure it has been assumed that the major regioisomers are substituted at the less hindered 3-position, by analogy to the products obtained in the reaction with phenyl boronic acid.

(*E*)-2-Phenylvinylboronic acid gave a single regioisomer, the reasons for which are unclear as it could be expected that regioselectivity of the cross-coupling would be controlled by the regioselectivity of the initial oxidative addition of tetrachloropyridazine to the palladium complex, which should be independent of the boronic acid used. This would suggest that isomerisation of the intermediate formed by oxidative addition is possible and that the reaction is under thermodynamic control. Therefore, it may be the case that (*E*)-2-phenylvinylboronic acid is a more sterically demanding boronic acid and forces cross-coupling to occur exclusively at the less hindered position.

No conversion was obtained with cyano and dimethylamino substituted aryl boronic acids or with thiophene boronic acid. It is not clear as to why this particular range of boronic acids should fail to give any cross-coupled product and suggests that this process is particularly sensitive to conditions and more research needs to be carried out to develop these reactions into generally applicable processes. For example, a range of bulky, electron-rich phosphine ligands are available for the efficient cross-coupling of chloro-heteroaromatics.

Boronic Acid	Conversion (%)	% 3- isomer ^a	% 4- isomer ^a	Isomer Ratio ^b
	0	-	-	
	0	-	-	
	100	 312a, 24%^c	 312b[*]	65 : 35
	0	-	-	
	100	 313a, 33%^c	-	100 : 0

^a Isolated Yields^b Isomer Ratios determined by integration of crude ¹H NMR spectra^c Isolated yields of product contaminated with Ph₃P and Ph₃P=O^{*} Not isolated

Table 5.4

5.7 Conclusions

Tetrachloropyridazine has been used as a scaffold for the synthesis of polysubstituted systems, however it appears to be less useful than tetrafluoropyridazine. Monosubstitution reactions with amines proceed with high regioselectivity at the 4-

position, but a second displacement of chlorine requires forcing microwave conditions and often proceeds with low regioselectivity.

Formation of cyclic systems is less efficient than the analogous reactions of tetrafluoropyridazine, proceeding with less regiocontrol, and the cyclisation step did not proceed in the case of amidines.

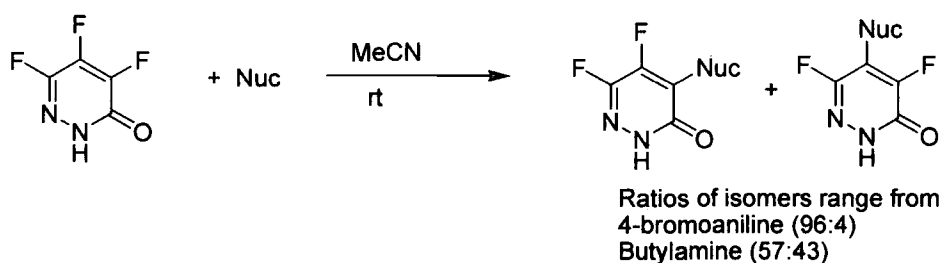
Attempted metallation of tetrachloropyridazine did not proceed, whilst palladium catalysed cross-coupling reactions appeared to be very sensitive towards the substrate used and require more work to obtain a more general process.

Chapter 6

Conclusions

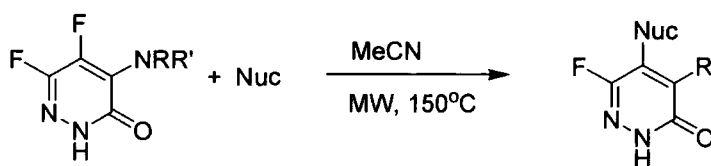
This thesis has described the synthesis of a range of polyfunctional systems from the perfluorinated heteroaromatic tetrafluoropyridazine by nucleophilic aromatic substitution of ring fluorine atoms. Such heterocyclic systems are likely to be of great interest in applications ranging from pharmaceuticals to materials.

4,5,6-Trifluoropyridazin-3(2*H*)-one has been shown to be an excellent scaffold for the production of amine substituted pyridazin-3(2*H*)-one derivatives (Scheme 6.1). Substitution occurs at the two fluorine atoms *para* to activating ring nitrogen, with selectivity for the 4-position generally increasing as the 'soft' electronic character of the nucleophile is increased. In the case of aromatic amine nucleophiles regioselectivity in favour of the 4-isomer can be as high as 95 : 5, however, in cases where the regioselectivity is lower separation of the two isomers is readily achieved by chromatography and gives access to both 4- and 5-substituted isomers.



Scheme 6.1

A second sequential substitution on 4-substituted 5,6-difluoropyridazin-3(2*H*)-ones proceeds regioselectively at the 4-position with a range of amine nucleophiles (Scheme 6.2), except in the case of displacement reactions on 4-(primary amino) substituted systems, which did not proceed to any useful extent. This was most likely because of better orbital overlap in the less sterically demanding primary amino systems, which rendered a primary amine substituent a more efficient electron donor and therefore more deactivating.

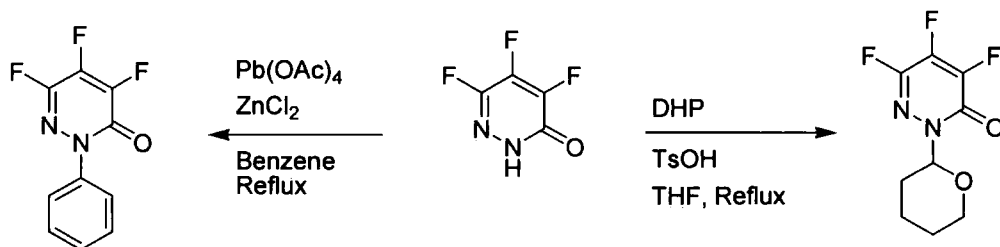


R = Morpholino, 4-bromoanilino Yields 15 - 90%

If R = Primary amino reaction fails

Scheme 6.2

Alkoxide nucleophiles failed to give useful yields of isolable products, which was thought to be due to their basicity leading to deprotonation of the pyridazin-3(2H)-one ring NH. As such, a strategy for protection of this site was sought and two synthetically viable routes were found (Scheme 6.3). Firstly, an *N*-arylation using lead(IV) acetate in benzene, and also protection as an *N*-(tetrahydropyranyl) derivative. In both cases the protecting group was found to have a minimum influence on regioselectivities and yields of substitution processes. Deprotection of the THP derivative is also feasible under standard conditions. This protecting group strategy has expanded the range of potential nucleophiles that are compatible with polyfluoropyridazin-3(2H)-one systems to more basic systems such as alkoxides.

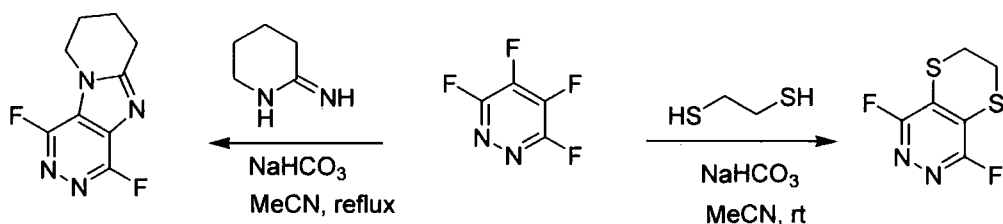


Scheme 6.3

This sequential nucleophilic displacement methodology has been shown to have the potential to synthesise a range of 6-fluoro-disubstituted pyridazin-3(2H)-ones. Furthermore, it has been shown that parallel synthesis techniques are appropriate for use in these reactions, allowing the rapid synthesis of a diverse range of compounds, which will be extremely useful in the lead generation stage of drug discovery.

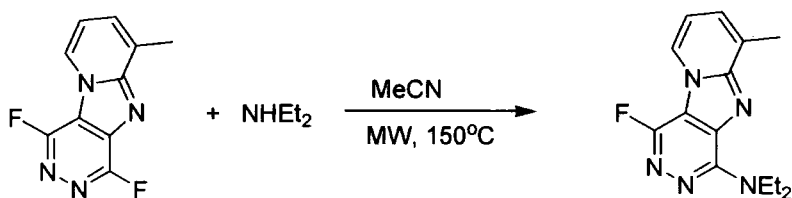
The reaction of difunctional nucleophiles with tetrafluoropyridazine has allowed the synthesis of various ring fused systems, many of which are novel core scaffolds (Scheme

6.4). Several [6,6]-ring fused systems have been synthesised by reaction with diamine, diol and dithiol derivatives, whilst [5,6]-ring fused systems have been obtained by reaction with amidine, thioamide and 2-aminopyridine derivatives.



Scheme 6.4

The ring fused scaffolds possess additional ring fluorine atoms that in the majority of cases are susceptible to regioselective displacement reactions (Scheme 6.5). In certain cases displacement of all ring fluorine atoms is possible to give non-halogenated products.

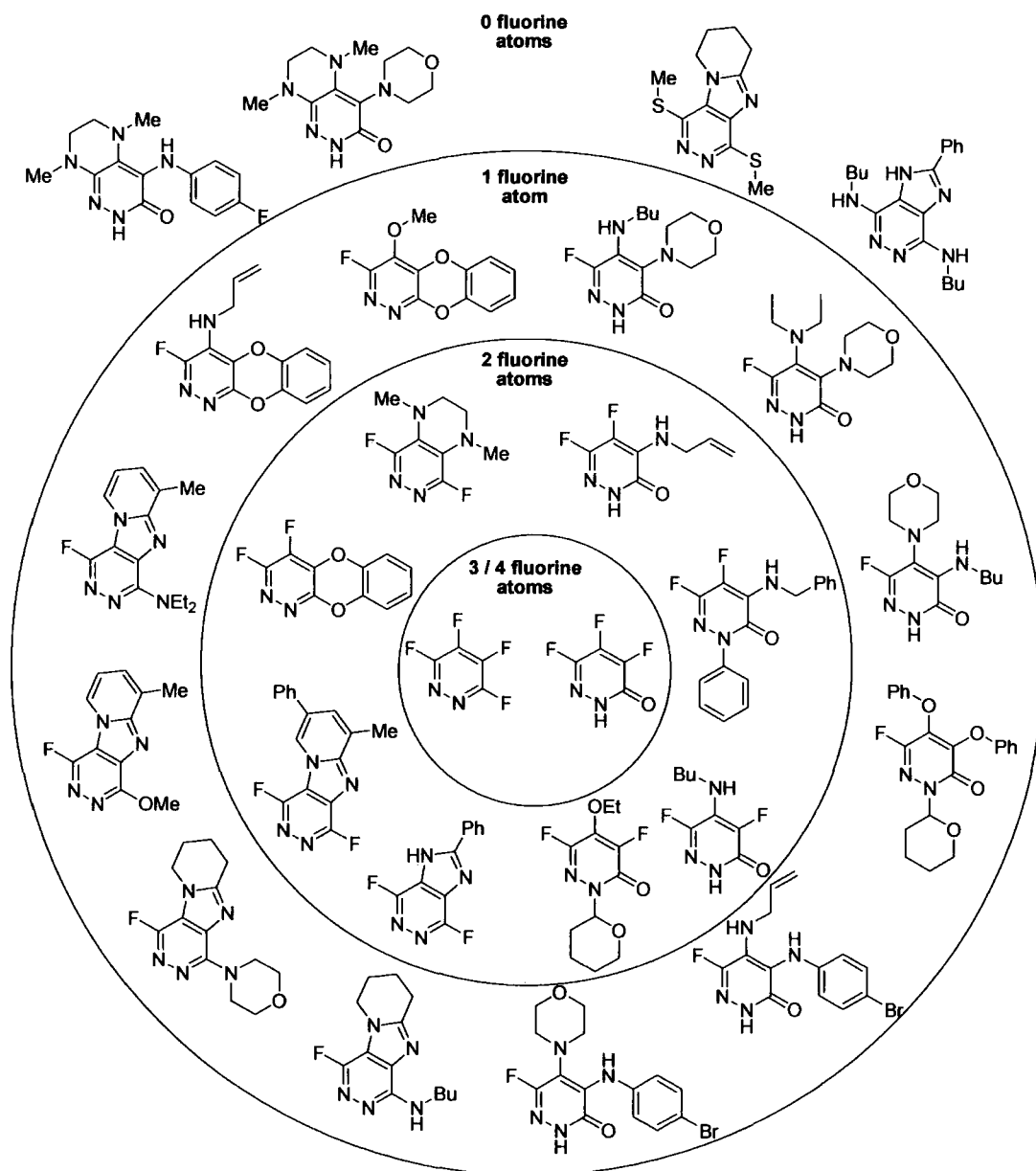


Scheme 6.5

The variety of dinucleophiles that are available will enable this strategy to be used for the synthesis of a range of heterocyclic species with moderate structural diversity, whilst substituent diversity can be increased by reaction of the scaffolds produced with a range of functionalised nitrogen, oxygen, sulfur and carbon nucleophiles. Again, the amenability of this approach to parallel synthesis methodology will allow for the synthesis of libraries of compounds based on different core scaffolds, which will be of significant interest to the development of medicinal chemistry programmes.

Calculations performed at GlaxoSmithKline on many of the compounds described in this thesis show that they fit the 'Lipinski guidelines' which describe the lipophilicity, hydrogen bond properties and molecular weight of a potential successful drug candidate. The results of these calculations are provided in Appendix 2 on the attached CD-ROM.

Overall, this strategy of sequential fluorine displacement in polyfluorinated heteroaromatics has been shown to have great potential for the synthesis of polyfunctional systems (Scheme 6.6) and is a versatile approach for the synthesis of diverse heterocyclic derivatives which are highly desired in a range of applications.



Scheme 6.6

Chapter 7

Experimental

7.1 Technical Detail

Reagents

Tetrafluoropyridazine was obtained from ABCR, whilst all starting materials were obtained commercially (Sigma-Aldrich, Alfa-Aesar) or from GlaxoSmithKline's chemical stores, Stevenage and used without further purification. Solvents were dried using either literature procedures or *via* the Innovative Technology solvent purification system.

Reactions and Purification

Reactions were performed under an atmosphere of argon gas using dry solvents. Microwave reactions were performed on a Biotage Initiator 60 EXP. Reactions were monitored by ^{19}F NMR or TLC on silica gel TLC plates.

Chromatography

Column chromatography was carried out on silica gel (Fluorochem, Merck no. 109385, particle size 0.040 – 0.063nm) unless otherwise stated or using a Biotage Horizon or Isco Companion flash chromatography system using pre-packed silica columns. Mass directed HPLC was performed on a Supelco LCABZ++ column using MicroMass MassLynx v4.0 software.

Melting Points

Melting points were recorded using a Gallenkamp melting point apparatus at atmospheric pressure and are uncorrected.

Infra-Red Spectroscopy

IR spectra were obtained using a Perkin Elmer 1600 Series FTIR using a Golden Gate attachment and analysed using GRAMS Analyst software.

NMR Spectroscopy

NMR spectra were recorded in the deuterated solvent stated, using tetramethylsilane and trichlorofluoromethane as an internal references on a Varian Mercury 400, Bruker Avance 400 or Bruker DPX400 operating at 400MHz (^1H NMR), 376MHz (^{19}F NMR) and 100MHz (^{13}C NMR), or a Varian Inova 500 operating at 500MHz (^1H NMR), 470MHz (^{19}F NMR) and 125MHz (^{13}C NMR), or a Varian VNMRS-700 operating at 700MHz (^1H NMR), 658MHz (^{19}F NMR) and 175MHz (^{13}C NMR). Chemical shifts are given in ppm and coupling constants are recorded in Hertz.

Mass Spectrometry

Mass spectra were recorded on a Thermoquest Trace GC-MS spectrometer (in electron ionisation mode), a Micromass LCT LC-MS spectrometer (in electrospray ES^+ mode) or a Waters ZQ mass spectrometer coupled to a Waters Acquity HPLC system (operating in electrospray positive or negative mode). Exact mass measurements were performed on a Thermo-Finnigan LTQ-FT spectrometer, a Bruker Daltonics 7T FTICR-MS or a Micromass Q-TOF hybrid quadrupole mass spectrometer, operating in electrospray positive mode.

Gas / Liquid Chromatography

Gas chromatography was carried out on a Thermo TRACE GC. Analytical HPLC was performed on an Analytical Varian LC (5ml/min).

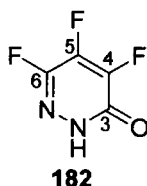
Elemental Analysis

Elemental analyses were obtained using an Exeter Analytical E-440 Elemental Analyser, or by Butterworth Laboratories Ltd., Teddington, UK.

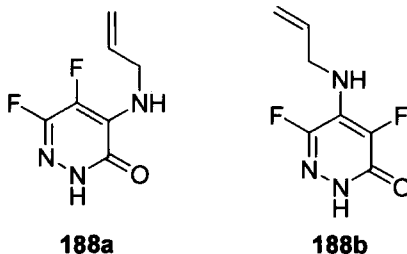
X-ray Crystallography

All crystallographic data was collected on a Bruker SMART-6000 CCD ($\lambda\text{MoK}\alpha$, ω -scan, 0.3° / frame) at $T = 120\text{K}$. The structures were solved using direct methods and refined by full-matrix least squares on F^2 for all data using SHELXTL software. All non-hydrogen atoms were refined with anisotropic displacement parameters, H-atoms were located on the difference map and refined-isotropically.

7.2 Experimental to Chapter 2

4,5,6-Trifluoropyridazin-3(2H)-one **182**

Tetrafluoropyridazine (1.20g, 7.89mmol) was dissolved in concentrated sulfuric acid (12ml) at 0°C. Water (48ml) was added dropwise using a dropping funnel, after which the mixture was allowed to warm to room temperature and was stirred for 1.5 hours. After this period the mixture was extracted with diethyl ether (3 × 25ml), and the organic extracts washed with saturated sodium sulfate solution (25ml), before being dried (MgSO₄), filtered and evaporated to yield a crude cream solid, which was recrystallised from toluene to yield 4,5,6-trifluoropyridazin-3(2H)-one¹³³ **182** (1.07 g, 90%) as white crystals; δ_{H} (300 MHz, CDCl₃) 11.4 – 11.8 (1H, br s, NH), 1.80 (1H, br s, OH); δ_{F} (282 MHz, CDCl₃) -101.7 (1F, dd, ³J_{FF} 25.7, ⁴J_{FF} 16.2, F6), -136.9 (1F, dd, ³J_{FF} 15.5, ⁴J_{FF} 16.2, F4), -143.5 (1F, dd, ³J_{FF} 25.7, ³J_{FF} 15.5, F5); *m/z* (EI⁺) 151 ([M]⁺, 5%), 150 ([M-H]⁺, 97), 122 (25), 121 (21), 93 (100), 74 (68), 31 ([CF]⁺, 100). Crystals suitable for X-ray diffraction were grown from slow evaporation of dichloromethane.

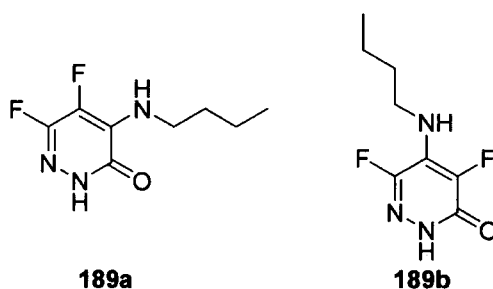
4-(Allylamino)-5,6-difluoropyridazin-3(2H)-one **188a** and 5-(allylamino)-4,6-difluoropyridazin-3(2H)-one **188b**

Allylamine (0.100ml, 1.33mmol) was mixed with 4,5,6-trifluoropyridazin-3(2H)-one (100mg, 0.666mmol) in a Radleys Greenhouse tube under nitrogen. Acetonitrile (5ml) was added and the mixture stirred at room temperature for 48 hours. After this period the

solvent was evaporated, and the residue dissolved in dichloromethane (10ml). Water (10ml) was added and the organic layer separated on a hydrophobic frit. The aqueous layer was then extracted with further portions of dichloromethane ($2 \times 10\text{ml}$). The combined organic extracts were dried (MgSO_4), filtered and evaporated on a blowdown evaporator, followed by purification by flash column chromatography (elutant cyclohexane : ethyl acetate 5:1 to 2:1 gradient over 20 minutes) to yield *4-(allylamino)-5,6-difluoropyridazin-3(2H)-one* **188a** (0.050g, 40%) as a white solid; mp $103 - 105^\circ\text{C}$ (Found $[\text{MH}]^+$ 188.06294. $\text{C}_7\text{H}_7\text{F}_2\text{N}_3\text{O}$ requires $[\text{MH}]^+$ 188.06299); $\nu_{\text{max}} / \text{cm}^{-1}$ 1072, 1139, 1292, 1367, 1453, 1587, 1640 (CO amide), 2859 (br, NH), 3293 (CH); δ_{H} (400MHz, CDCl_3) 4.14 (2H, ddd, $^3J_{\text{HH}}$ 6.2, 6.0, $^5J_{\text{HF}}$ 1.8, $\text{NHCH}_2\text{CH}=\text{CH}_2$), 5.24 (1H, dd, $^3J_{\text{HH}}$ 10.3, $^2J_{\text{HH}}$ 1.3, $\text{NHCH}_2\text{CH}=\text{CH}_2$), 5.27 (1H, dd, $^3J_{\text{HH}}$ 15.6, $^2J_{\text{HH}}$ 1.3, $\text{NHCH}_2\text{CH}=\text{CH}_2$), 5.62 (1H, br t, $^3J_{\text{HH}}$ 6.0 $\text{NHCH}_2\text{CH}=\text{CH}_2$), 5.93 (1H, ddt, $^3J_{\text{HH}}$ 15.6, 10.3, 6.0, $\text{NHCH}_2\text{CH}=\text{CH}_2$), 11.00 (1H, br s, ring NH); δ_{C} (100MHz, CDCl_3) 46.3 (d, $^4J_{\text{CF}}$ 6.4, $\text{NHCH}_2\text{CH}=\text{CH}_2$), 117.1 (s, $\text{NHCH}_2\text{CH}=\text{CH}_2$), 131.2 (dd, $^1J_{\text{CF}}$ 260.4, $^2J_{\text{CF}}$ 32.8, C5), 131.8 (d, $^2J_{\text{CF}}$ 8.8, C4), 133.6 (d, $^5J_{\text{CF}}$ 1.6, $\text{NHCH}_2\text{CH}=\text{CH}_2$), 149.0 (dd, $^1J_{\text{CF}}$ 230.9, $^2J_{\text{CF}}$ 17.6, C6), 159.8 (d, $^3J_{\text{CF}}$ 11.2, C3); δ_{F} (376MHz, CDCl_3) -106.1 (1F, d, $^3J_{\text{FF}}$ 26.4, F6), -161.9 (1F, d, $^3J_{\text{FF}}$ 26.4, F5); m/z (ES^-) 186 (100%, $[\text{M}-\text{H}]^-$).

The minor isomer *5-(allylamino)-4,6-difluoropyridazin-3(2H)-one* **188b** was also obtained (0.0168g, 13%) as a white solid; mp $143 - 144^\circ\text{C}$ (Found $[\text{MH}]^+$ 188.06304. $\text{C}_7\text{H}_7\text{F}_2\text{N}_3\text{O}$ requires $[\text{MH}]^+$ 188.06299); $\nu_{\text{max}} / \text{cm}^{-1}$ 998, 1040, 1099, 1166, 1363, 1432, 1525, 1589, 1621 (CO amide), 2853 (br, NH), 3278 (CH); δ_{H} (600MHz, MeOD) 4.02 (2H, dd, $^3J_{\text{HH}}$ 5.1, $^5J_{\text{HF}}$ 1.5, $\text{NHCH}_2\text{CH}=\text{CH}_2$), 5.16 (1H, d, $^3J_{\text{HH}}$ 10.3, $\text{NHCH}_2\text{CH}=\text{CH}_2$), 5.22 (1H, d, $^3J_{\text{HH}}$ 17.2, $\text{NHCH}_2\text{CH}=\text{CH}_2$), 5.93 (1H, ddt, $^3J_{\text{HH}}$ 17.2, 10.3, 5.1, $\text{NHCH}_2\text{CH}=\text{CH}_2$); δ_{C} (151MHz, MeOD) 47.0 (d, $^4J_{\text{CF}}$ 6.6, $\text{NHCH}_2\text{CH}=\text{CH}_2$), 116.5 (s, $\text{NHCH}_2\text{CH}=\text{CH}_2$), 129.6 (dd, $^2J_{\text{CF}}$ 29.9, $^2J_{\text{CF}}$ 6.7, C5), 135.9 (d, $^5J_{\text{CF}}$ 2.2, $\text{NHCH}_2\text{CH}=\text{CH}_2$), 139.8 (dd, $^1J_{\text{CF}}$ 241.0, $^3J_{\text{CF}}$ 11.1, C4), 149.4 (dd, $^1J_{\text{CF}}$ 232.2, $^3J_{\text{CF}}$ 11.1, C6), 158.8 (d, $^2J_{\text{CF}}$ 22.1, C3); δ_{F} (376MHz, MeOD) -102.0 (1F, d, $^4J_{\text{FF}}$ 24.7, F6), -156.6 (1F, d, $^4J_{\text{FF}}$ 24.7, F5); m/z (ES^+) 188 (100%, $[\text{M}+\text{H}]^+$), 229 (29, $[\text{M}+\text{MeCN}]^+$).

4-(Butylamino)-5,6-difluoropyridazin-3(2H)-one **189a** and 5-(butylamino)-4,6-difluoropyridazin-3(2H)-one **189b**

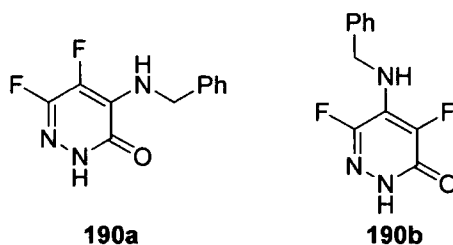


4,5,6-Trifluoropyridazin-3(2H)-one (0.50g, 3.33mmol) was dissolved in acetonitrile (20 ml) under argon with stirring. *n*-Butylamine (0.66ml, 6.66mmol) was added dropwise, and the mixture stirred at room temperature for 5 hours. After this period water (20ml) was added followed by dichloromethane (20 ml), and the organic layer separated. The aqueous layer was then extracted with further portions of dichloromethane (2 × 20ml), and the combined organic extracts were dried (MgSO₄), filtered and evaporated under vacuum to yield a crude yellow product (0.59g), containing 2 products in a 56:44 ratio by ¹⁹F NMR analysis. These were then purified by flash column chromatography with ethyl acetate and hexane as elutant (1:2 900ml, followed by 1:1 500ml) to yield the major product 4-(butylamino)-5,6-difluoropyridazin-3(2H)-one **189a** (0.28g, 41%) as white crystals; mp 80 – 81°C (Found C, 47.3; H, 5.5; N, 20.6; C₈H₁₁N₃F₂O requires C, 47.3; H, 5.5; N, 20.7%); ν_{\max} / cm⁻¹ 1030, 1112, 1281, 1378, 1448, 1587, 1644 (CO amide), 2963 (br, NH), 3286 (CH); δ_{H} (500MHz, CDCl₃) 0.95 (3H, t, ³J_{HH} 7.4, NHCH₂CH₂CH₂CH₃), 1.40 (2H, sextet, ³J_{HH} 7.4, NHCH₂CH₂CH₂CH₃), 1.62 (2H, pent, ³J_{HH} 7.4, NHCH₂CH₂CH₂CH₃), 3.51 (2H, qd, ³J_{HH} 7.0, ⁵J_{HF} 2.7, NHCH₂CH₂CH₂CH₃), 5.53 (1H, br t, ³J_{HH} 7.0, NHBu), 11.60 (1H, br s, ring NH); δ_{C} (125MHz, CDCl₃) 13.8 (s, NHCH₂CH₂CH₂CH₃), 19.9 (s, NHCH₂CH₂CH₂CH₃), 32.6 (d, ⁵J_{CF} 2.2, NHCH₂CH₂CH₂CH₃), 44.0 (d, ⁴J_{CF} 5.9, NHCH₂CH₂CH₂CH₃), 130.8 (dd, ¹J_{CF} 258.9, ²J_{CF} 32.5, C5), 132.3 (d, ²J_{CF} 8.7, C4), 149.4 (dd, ¹J_{CF} 230.4, ²J_{CF} 17.0, C6), 160.2 (d, ³J_{CF} 11.3, C3); δ_{F} (376MHz, CDCl₃) -106.8 (1F, d, ³J_{FF} 27.4, F6), -163.5 (1F, d, ³J_{FF} 27.4, F5); *m/z* (EI⁺) 203 (14%, [M]⁺), 160 (100, [M-Pr]⁺), 147 (29, [M-Bu]⁺).

The minor isomer was identified as 5-(butylamino)-4,6-difluoropyridazin-3(2H)-one **189b**, (0.21g, 31%) as white crystals; mp 143 – 144°C (Found C, 47.2; H, 5.4; N, 20.7; C₈H₁₁N₃F₂O requires C, 47.3; H, 5.5; N, 20.7%); ν_{\max} / cm⁻¹ 1008, 1115, 1158, 1287, 1375,

1439, 1529, 1590, 1643 (CO amide), 2959 (br, NH), 3283 (CH); δ_{H} (500MHz, $(\text{CD}_3)_2\text{CO}$) 0.93 (3H, t, $^3J_{\text{HH}}$ 7.4, $\text{NHCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 1.40 (2H, sextet, $^3J_{\text{HH}}$ 7.4, $\text{NHCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 1.63 (2H, pent, $^3J_{\text{HH}}$ 7.1, $\text{NHCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 3.47 (2H, qd, $^3J_{\text{HH}}$ 7.1, $^5J_{\text{HF}}$ 2.8, $\text{NHCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 5.93 (1H, br s, NHBu), 11.93 (1H, br s, ring NH); δ_{C} (125MHz, $(\text{CD}_3)_2\text{CO}$) 14.0 (s, $\text{NHCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 20.4 (s, $\text{NHCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 33.3 (d, $^5J_{\text{CF}}$ 2.8, $\text{NHCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 44.6 (d, $^4J_{\text{CF}}$ 6.8, $\text{NHCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 128.4 (dd, $^2J_{\text{CF}}$ 31.3, $^2J_{\text{CF}}$ 6.7, C5), 139.4 (dd, $^1J_{\text{CF}}$ 241.7, $^3J_{\text{CF}}$ 12.0, C4), 148.2 (dd, $^1J_{\text{CF}}$ 230.0, $^3J_{\text{CF}}$ 10.4, C6), 157.0 (d, $^2J_{\text{CF}}$ 22.6, C3); δ_{F} (376MHz, CDCl_3) -101.9 (1F, d, $^4J_{\text{FF}}$ 23.5, F6), -153.5 (1F, $^4J_{\text{FF}}$ 23.5, F5); m/z (ES^+) 204 (100%, $[\text{M}+\text{H}]^+$), 245 (19, $[\text{M}+\text{MeCN}]^+$). Crystals suitable for X-ray diffraction obtained by recrystallisation from acetonitrile.

4-(Benzylamino)-5,6-difluoropyridazin-3(2H)-one **190a** and 5-(benzylamino)-4,6-difluoropyridazin-3(2H)-one **190b**

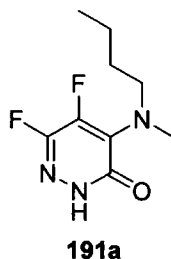


4,5,6-Trifluoropyridazin-3(2H)-one (0.50g, 3.33mmol) was dissolved in acetonitrile (20ml) under argon with stirring. Benzylamine (0.72ml, 6.66mmol) was added dropwise, and the mixture stirred at room temperature for 16 hours. After this period water (20ml) was added followed by dichloromethane (20ml), and the organic layer separated. The aqueous layer was then extracted with further portions of dichloromethane (2 × 20ml), and the combined organic extracts were dried (MgSO_4), filtered and evaporated under vacuum to yield a crude yellow product (0.72g), containing 2 products in a 61:39 ratio by ^{19}F NMR analysis. These were then purified by flash column chromatography with ethyl acetate and hexane as elutant (1:2 900ml, followed by 1:1 500ml) to yield the major product 4-(benzylamino)-5,6-difluoropyridazin-3(2H)-one **190a** (0.39g, 49%) as a white solid; mp 146 – 147°C (Found C, 55.8; H, 3.9; N, 17.5. $\text{C}_{11}\text{H}_9\text{N}_3\text{F}_2\text{O}$ requires C, 55.7; H, 3.8; N, 17.7%); ν_{max} / cm^{-1} 1023, 1073, 1123, 1274, 1377, 1449, 1507, 1581, 1636 (CO amide), 2988 (br, NH), 3377; δ_{H} (500MHz, CDCl_3) 4.69 (2H, dd, $^3J_{\text{HH}}$ 6.6, $^4J_{\text{HH}}$ 2.2, NHCH_2Ph), 5.88 (1H, br t, $^3J_{\text{HH}}$ 6.6, NHBn), 7.38 – 7.30 (5H, m, Ar-H), 11.37 (1H, br s, ring NH); δ_{C}

(125MHz, CDCl₃) 48.3 (d, ⁴J_{CF} 6.3, CH₂), 127.6 (s, ArC), 128.3 (s, ArC), 129.2 (s, ArC), 132.0 (d, ³J_{CF} 8.6, C4), 131.7 (dd, ¹J_{CF} 256.3, ²J_{CF} 32.4, C5), 137.8 (s, C1'), 149.2 (dd, ¹J_{CF} 229.8, ²J_{CF} 17.7, C6), 160.1 (d, ³J_{CF} 11.7, C3); δ_F (376MHz, CDCl₃) -105.9 (1F, d, ³J_{FF} 27.5, F6), -161.1 (1F, d, ³J_{FF} 27.5, F5); *m/z* (EI⁺) 237 (53%, [M]⁺), 91 (100, [CH₂Ph]⁺), 65 (63). Crystals suitable for X-ray diffraction obtained by recrystallisation from acetonitrile.

The minor product required further purification by recrystallisation from acetonitrile, and was shown to be 5-(benzylamino)-4,6-difluoropyridazin-3(2H)-one **190b** (0.23g, 29%) as a white solid; mp 175 – 176°C (Found C, 55.6; H, 3.9; N, 17.6. C₈H₁₁N₄FO requires C, 55.7; H, 3.8; N, 17.5%); δ_H (500MHz, CDCl₃) 4.50 (1H, br s, NH), 4.67 (2H, dd, ³J_{HH} 6.3, ⁴J_{HF} 2.5, CH₂), 7.31 – 7.42 (5H, m, ArH), 10.63 (1H, br s, ring NH); δ_C (100MHz, DMSO-d₆) 46.5 (d, ⁴J_{CF} 6.5, CH₂), 126.6 (s, ArC), 127.0 (s, ArC), 127.0 (dd, ²J_{CF} 31.3, 6.9, C5), 128.4 (s, ArC), 138.3 (dd, ¹J_{CF} 241.4, ³J_{CF} 12.1, C4), 139.4 (d, ⁵J_{CF} 1.8, C1'), 146.9 (dd, ¹J_{CF} 230.8, ³J_{CF} 10.3, C6), 155.7 (d, ²J_{CF} 22.0, C3); δ_F (376MHz, CDCl₃) -101.3 (1F, d, ⁴J_{FF} 22.9, F6), -150.9 (1F, d, ⁴J_{FF} 22.9, F4); *m/z* (EI⁺) 237 (12%, [M]⁺), 91 (100, [CH₂Ph]⁺).

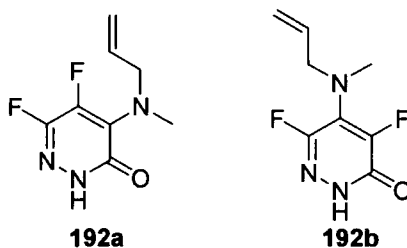
4-(*N*-Butyl-*N*-methylamino)-5,6-difluoropyridazin-3(2H)-one **191a**



N-methylbutylamine (0.158ml, 1.33mmol) was mixed with 4,5,6-trifluoropyridazin-3(2H)-one (100mg, 0.666mmol) in a Radleys Greenhouse tube under nitrogen. Acetonitrile (5ml) was added and the mixture stirred at room temperature for 16 hours. After this period the solvent was evaporated, and the residue dissolved in dichloromethane (10ml). Water (10ml) was added and the organic layer separated on a hydrophobic frit. The aqueous layer was then extracted with further portions of dichloromethane (2 × 10ml). The combined organic extracts were dried (MgSO₄), filtered and evaporated on a blowdown evaporator to yield crude material which was purified by flash column chromatography (Elutant ethyl acetate : hexane – gradient 10% to 33% EtOAc over 20 minutes) to yield 4-(*N*-butyl-*N*-methylamino)-5,6-difluoropyridazin-3(2H)-one **191a** (0.067g, 46%) as a white

solid; mp 78 – 79°C (Found $[\text{MH}]^+$ 218.10998. $\text{C}_9\text{H}_{13}\text{F}_2\text{N}_3\text{O}$ requires $[\text{MH}]^+$ 218.10994); δ_{H} (400MHz, CDCl_3) 0.93 (3H, t, $^3J_{\text{HH}}$ 7.5, $\text{NCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 1.32 (2H, sextet, $^3J_{\text{HH}}$ 7.5, $\text{NCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 1.61 (2H, pent, $^3J_{\text{HH}}$ 7.5, $\text{NCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 3.17 (3H, d, $^5J_{\text{HF}}$ 4.8, NMeBu), 3.56 (2H, td, $^3J_{\text{HH}}$ 7.5, $^5J_{\text{HF}}$ 1.0, $\text{NCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 11.41 (1H, br s, ring NH); δ_{C} (100MHz, CDCl_3) 13.8 (s, $\text{NCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 19.8 (s, $\text{NCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 30.4 (d, $^5J_{\text{CF}}$ 1.6, $\text{NCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 40.0 (d, $^4J_{\text{CF}}$ 6.4, NMeBu), 53.4 (d, $^4J_{\text{CF}}$ 4.0, $\text{NCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 135.3 (d, $^2J_{\text{CF}}$ 8.0, C4), 136.5 (dd, $^1J_{\text{CF}}$ 264.4, $^2J_{\text{CF}}$ 32.0, C5), 149.0 (dd, $^1J_{\text{CF}}$ 231.7, $^2J_{\text{CF}}$ 19.2, C6), 161.6 (d, $^3J_{\text{CF}}$ 9.6, C3); δ_{F} (376MHz, CDCl_3) -107.7 (1F, d, $^3J_{\text{FF}}$ 26.4, F6), -149.4 (1F, $^3J_{\text{FF}}$ 26.4, F5); m/z (ES^+) 218 (100%, $[\text{M}+\text{H}]^+$).

4-(N-Allyl-N-methylamino)-5,6-difluoropyridazin-3(2H)-one 192a and *5-(N-allyl-N-methylamino)-4,6-difluoropyridazin-3(2H)-one 192b*

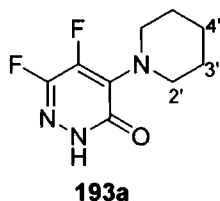


N-Methylallylamine (0.127ml, 1.33mmol) was mixed with 4,5,6-trifluoropyridazin-3(2H)-one (100mg, 0.666mmol) in a Radleys Greenhouse tube under nitrogen. Acetonitrile (5ml) was added and the mixture stirred at room temperature for 48 hours. After this period the solvent was evaporated, and the residue dissolved in dichloromethane (10ml). Water (10ml) was added and the organic layer separated on a hydrophobic frit. The aqueous layer was then extracted with further portions of dichloromethane ($2 \times 10\text{ml}$). The combined organic extracts were dried (MgSO_4), filtered and evaporated on a blowdown evaporator, followed by purification by flash column chromatography (elutant cyclohexane : ethyl acetate 5:1 to 2:1 gradient over 20 minutes) to yield *4-(N-allyl-N-methylamino)-5,6-difluoropyridazin-3(2H)-one 192a* (0.066g, 49%) as a white solid; mp 95 – 96°C (Found $[\text{MH}]^+$ 202.07859. $\text{C}_8\text{H}_9\text{F}_2\text{N}_3\text{O}$ requires $[\text{MH}]^+$ 202.07864); ν_{max} / cm^{-1} 996, 1074, 1116, 1177, 1251, 1416, 1482, 1564, 1626 (CO amide), 2921 (br, NH); δ_{H} (400MHz, CDCl_3) 3.14 (3H, d, $^5J_{\text{HF}}$ 4.7, NCH_3), 4.14 (2H, dd, $^3J_{\text{HH}}$ 6.0, $^5J_{\text{HF}}$ 1.0, $\text{NCH}_2\text{CH}=\text{CH}_2$), 5.24 (1H, d, $^3J_{\text{HH}}$ 16.0, $\text{NCH}_2\text{CH}=\text{CH}_2$), 5.24 (1H, d, $^3J_{\text{HH}}$ 11.6, $\text{NCH}_2\text{CH}=\text{CH}_2$) 5.90 (1H, ddt, $^3J_{\text{HH}}$ 16.0, 11.6, 6.0, $\text{NCH}_2\text{CH}=\text{CH}_2$), 10.66 (1H, br s, ring NH); δ_{C} (100MHz, CDCl_3) 39.4 (d,

$^4J_{CF}$ 6.4, NCH_3), 55.9 (d, $^4J_{CF}$ 2.8, $NCH_2CH=CH_2$), 118.0 (s, $NCH_2CH=CH_2$), 133.9 (s, $NHCH_2CH=CH_2$), 135.0 (d, $^2J_{CF}$ 7.2, C5), 137.0 (dd, $^1J_{CF}$ 265.2, $^2J_{CF}$ 31.2, C4), 149.0 (dd, $^1J_{CF}$ 232.5, $^2J_{CF}$ 19.2, C6), 161.6 (d, $^3J_{CF}$ 9.6, C3); δ_F (376MHz, $CDCl_3$) -107.5 (1F, d, $^3J_{FF}$ 26.7, F6), -148.4 (1F, dq, $^3J_{FF}$ 26.7, $^5J_{HF}$ 4.7, F5); m/z (ES^+) 202 (100%, $[M+H]^+$).

The minor isomer *5-(N-allyl-N-methylamino)-4,6-difluoropyridazin-3(2H)-one* **192b** was also obtained (0.0208g, 16%) as a white solid; mp 82 – 84°C (Found $[MH]^+$ 202.07865. $C_8H_9F_2N_3O$ requires MH^+ 202.07864); δ_H (400MHz, $CDCl_3$) 3.03 (3H, dd, $^5J_{HF}$ 4.0, 2.5, NCH_3), 3.85 (2H, d, $^3J_{HH}$ 6.0, $NHCH_2CH=CH_2$), 5.27 (3H, m, $NHCH_2CH=CH_2$), 5.85 (1H, m, $NHCH_2CH=CH_2$); δ_C (100MHz, $CDCl_3$) 39.4 (dd, $^4J_{CF}$ 5.6, 4.8, NCH_3) 57.2 (dd, $^4J_{CF}$ 5.6, 4.0, $NHCH_2CH=CH_2$), 118.9 (s, $NHCH_2CH=CH_2$), 130.8 (dd, $^2J_{CF}$ 28.0, 6.4, C5), 132.7 (s, $NHCH_2CH=CH_2$), 144.1 (dd, $^1J_{CF}$ 252.5, $^3J_{CF}$ 12.8, C4), 149.3 (dd, $^1J_{CF}$ 236.5, $^3J_{CF}$ 8.8, C6), 157.7 (d, $^2J_{CF}$ 23.2, C3); δ_F (376MHz, $CDCl_3$) -91.0 (1F, d, $^4J_{FF}$ 22.4, F6), -139.4 (1F, d, $^4J_{FF}$ 22.4, F4); m/z (ES^+) 202 (100%, $[M+H]^+$).

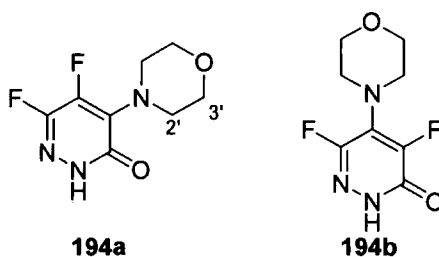
5,6-Difluoro-4-(piperidin-1-yl)pyridazin-3(2H)-one **193a**



Piperidine (0.132ml, 1.33mmol) was mixed with 4,5,6-trifluoropyridazin-3(2H)-one (100mg, 0.666mmol) in a Radleys Greenhouse tube under nitrogen. Acetonitrile (5ml) was added and the mixture stirred at room temperature for 48 hours. After this period the solvent was evaporated, and the residue dissolved in dichloromethane (10ml). Water (10ml) was added and the organic layer separated on a hydrophobic frit. The aqueous layer was then extracted with further portions of dichloromethane (2 × 10ml). The combined organic extracts were dried ($MgSO_4$), filtered and evaporated on a blowdown evaporator to yield crude material which was purified by flash column chromatography (elutant cyclohexane : ethyl acetate 4:1 to 2:1 gradient over 20 minutes), followed by mass directed automated purification to yield *5,6-difluoro-4-(piperidin-1-yl)pyridazin-3(2H)-one* **193a** (0.074g, 52%) as a white solid; mp 145 – 146°C (Found $[MH]^+$ 216.09426. $C_9H_{11}F_2N_3O$ requires $[MH]^+$ 216.09429); δ_H (400MHz, $CDCl_3$) 1.68 (6H, m, C3'(H) + C4'(H)), 3.54 (4H, m, C2'(H)), 11.08 (1H, br s, ring NH); δ_C (100MHz, $CDCl_3$) 24.2 (s, C4'), 26.5 (d,

$^5J_{CF}$ 1.6, C3'), 50.4 (d, $^4J_{CF}$ 4.8, C2'), 135.3 (d, $^2J_{CF}$ 7.2, C4), 137.4 (dd, $^1J_{CF}$ 265.2, $^2J_{CF}$ 31.2, C5), 148.9 (dd, $^1J_{CF}$ 232.5, $^2J_{CF}$ 19.2, C6), 160.9 (d, $^3J_{CF}$ 10.4, C3); δ_F (376MHz, $CDCl_3$) -107.4 (1F, d, $^4J_{FF}$ 27.0, F6), -147.6 (1F, $^4J_{FF}$ 27.0, F5); m/z (ES^+) 216 (100%, $[M+H]^+$).

5,6-Difluoro-4-morpholinopyridazin-3(2H)-one 194a and **4,6-difluoro-5-(4-morpholinyl)-3(2H)-pyridazinone 194b**

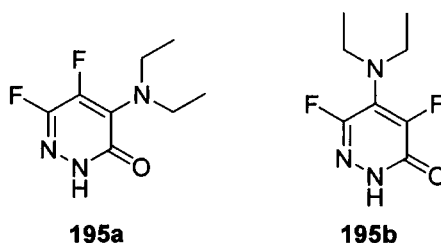


4,5,6-Trifluoropyridazin-3(2H)-one (0.50g, 3.33mmol) was dissolved in acetonitrile (20ml) under argon with stirring. Morpholine (0.58ml, 6.66mmol) was added dropwise, and the mixture stirred at room temperature for 4.5 hours. After this period water (20ml) was added followed by dichloromethane (20ml), and the organic layer separated. The aqueous layer was then extracted with further portions of dichloromethane (2×20 ml), and the combined organic extracts were dried ($MgSO_4$), filtered and evaporated under vacuum to yield a crude yellow product (0.59g). This was purified by recrystallisation from acetonitrile to yield **5,6-difluoro-4-morpholinopyridazin-3(2H)-one 194a** (0.42g, 59%) as white crystals; mp 179 – 180°C (Found C, 44.4; H, 4.2; N, 19.5. $C_8H_9N_3F_2O_2$ requires C, 44.2; H, 4.2; N, 19.4%); ν_{max} / cm^{-1} 1002, 1048, 1106, 1246, 1274, 1392, 1451, 1574, 1615, 1644 (CO amide), 2859 (br, NH), 3145; δ_H (400MHz, $DMSO-d_6$) 3.64 (4H, br t, $^3J_{HH}$ 4.5, C2'(H)), 3.81 (4H, t, $^3J_{HH}$ 4.5, C3'(H)), 10.33 (1H, br s, ring NH); δ_C (100MHz, $DMSO-d_6$) 48.8 (d, $^4J_{CF}$ 4.6, C2'), 66.5 (d, $^5J_{CF}$ 1.7, C3'), 133.9 (dd, $^2J_{CF}$ 7.2, $^3J_{CF}$ 2.3, C4), 137.0 (dd, $^1J_{CF}$ 264.8, $^2J_{CF}$ 32.7, C5), 147.4 (dd, $^1J_{CF}$ 226.8, $^2J_{CF}$ 19.2, C6), 159.8 (d, $^3J_{CF}$ 9.1, $^4J_{CF}$ 0.8, C3); δ_F (376MHz, $DMSO-d_6$) -109.3 (1F, d, $^3J_{FF}$ 29.5, F6), -149.0 (1F, $^3J_{FF}$ 29.5, F5); m/z (EI^+) 217 (16, $[M]^+$), 132 (100, $[M-morpholino]^+$).

The minor product, **4,6-difluoro-5-(4-morpholinyl)-3(2H)-pyridazinone 194b**, was also isolated by flash column chromatography with ethyl acetate and hexane (1:4) as eluant; (0.090g, 12%) as white crystals; mp 179 – 180°C (Found C, 44.2; H, 4.1; N, 19.1. $C_8H_9N_3F_2O_2$ requires C, 44.2; H, 4.2; N, 19.4%); ν_{max} / cm^{-1} 1219, 1368, 1450, 1639 (CO

amide), 3000 (br, NH); δ_{H} (400MHz, CDCl_3) 3.42 (4H, dt, $^3J_{\text{HH}}$ 5.8, $^5J_{\text{HF}}$ 2.0, C2'(H)), 3.81 (5H, t, $^3J_{\text{HH}}$ 4.8, C3'(H), OH underneath); δ_{C} (100MHz, CDCl_3) 50.3 (dd, $^4J_{\text{CF}}$ 4.0, C2'), 66.8 (d, $^5J_{\text{CF}}$ 1.6, C3'), 130.0 (dd, $^2J_{\text{CF}}$ 27.9, $^2J_{\text{CF}}$ 5.6, C5), 145.4 (dd, $^1J_{\text{CF}}$ 255.6, $^3J_{\text{CF}}$ 12.0, C4), 149.5 (dd, $^1J_{\text{CF}}$ 237.3, $^3J_{\text{CF}}$ 8.8, C6), 160.9 (d, $^2J_{\text{CF}}$ 23.2, C3); δ_{F} (376MHz, CDCl_3) -92.0 (1F, d, $^4J_{\text{FF}}$ 20.7, F6), -146.9 (1F, d, $^4J_{\text{FF}}$ 20.7, F4); m/z (ES^+) 218 (100%, $[\text{M}+\text{H}]^+$).

4-(Diethylamino)-5,6-difluoropyridazin-3(2H)-one **195a** and *5-(diethylamino)-4,6-difluoro-pyridazin-3(2H)-one* **195b**

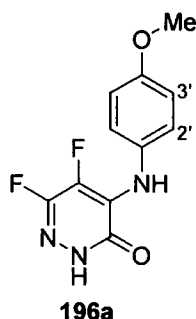


Diethylamine (0.138ml, 1.33mmol) was mixed with 4,5,6-trifluoropyridazin-3(2H)-one (100mg, 0.666mmol) in a Radleys Greenhouse tube under nitrogen. Acetonitrile (5ml) was added and the mixture stirred at room temperature for 16 hours. After this period the solvent was evaporated, and the residue dissolved in dichloromethane (10ml). Water (10ml) was added and the organic layer separated on a hydrophobic frit. The aqueous layer was then extracted with further portions of dichloromethane ($2 \times 10\text{ml}$). The combined organic extracts were dried (MgSO_4), filtered and evaporated on a blowdown evaporator to yield crude material which was purified by mass directed automated purification to yield *4-(diethylamino)-5,6-difluoropyridazin-3(2H)-one* **195a** (0.062g, 46%) as a white solid; mp $98 - 99^\circ\text{C}$, (Found $[\text{MH}]^+$ 204.09439. $\text{C}_8\text{H}_{11}\text{F}_2\text{N}_3\text{O}$ requires $[\text{MH}]^+$ 204.09429); $\nu_{\text{max}} / \text{cm}^{-1}$ 1046, 1186, 1450, 1661 (CO amide), 2900 (br, NH); δ_{H} (400MHz, CDCl_3) 1.22 (6H, t, $^3J_{\text{HH}}$ 7.0, NCH_2CH_3), 3.51 (4H, qd, $^3J_{\text{HH}}$ 7.0, $^5J_{\text{HF}}$ 1.8, NCH_2CH_3), 11.06 (1H, br s, ring NH); δ_{C} (100MHz, CDCl_3) 14.2 (d, $^5J_{\text{CF}}$ 2.4, NCH_2CH_3), 45.8 (d, $^4J_{\text{CF}}$ 4.8, NCH_2CH_3), 134.2 (d, $^2J_{\text{CF}}$ 7.2, C4), 136.5 (dd, $^1J_{\text{CF}}$ 263.6, $^2J_{\text{CF}}$ 31.2, C5), 149.1 (dd, $^1J_{\text{CF}}$ 230.9, $^2J_{\text{CF}}$ 19.2, C6), 161.5 (d, $^3J_{\text{CF}}$ 10.4, C3); δ_{F} (376MHz, CDCl_3) -108.1 (1F, d, $^3J_{\text{FF}}$ 27.0, F6), -149.2 (1F, $^3J_{\text{FF}}$ 27.0, F5); m/z (ES^+) 204 (100%, $[\text{M}+\text{H}]^+$).

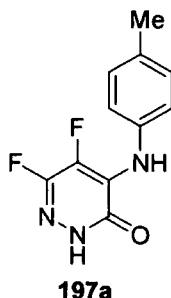
The minor isomer *5-(diethylamino)-4,6-difluoropyridazin-3(2H)-one* **195b** was also isolated (0.012g, 9%) as a white solid; mp $82 - 83^\circ\text{C}$ (Found $[\text{MH}]^+$ 204.09437. $\text{C}_8\text{H}_{11}\text{F}_2\text{N}_3\text{O}$ requires $[\text{MH}]^+$ 204.09429); $\nu_{\text{max}} / \text{cm}^{-1}$ 1094, 1200, 1397, 1457, 1571, 1631,

2874 (br); δ_{H} (400MHz, CDCl_3) 1.22 (6H, t, $^3\text{J}_{\text{HH}}$ 7.0, NCH_2CH_3), 3.37 (4H, q, $^3\text{J}_{\text{HH}}$ 7.0, NCH_2CH_3), 11.34 (1H, br s, ring NH); δ_{C} (100MHz, CDCl_3) 13.7 (s, NCH_2CH_3), 46.4 (dd, $^4\text{J}_{\text{CF}}$ 4.8, $^4\text{J}_{\text{CF}}$ 4.8, NCH_2CH_3), 129.8 (dd, $^2\text{J}_{\text{CF}}$ 28.8, $^2\text{J}_{\text{CF}}$ 7.2, C5), 144.1 (dd, $^1\text{J}_{\text{CF}}$ 252.5, $^3\text{J}_{\text{CF}}$ 12.8, C4), 149.6 (dd, $^1\text{J}_{\text{CF}}$ 237.3, $^3\text{J}_{\text{CF}}$ 9.6, C6), 157.4 (d, $^2\text{J}_{\text{CF}}$ 24.0, C3); δ_{F} (376MHz, CDCl_3) -91.2 (1F, d, $^4\text{J}_{\text{FF}}$ 22.4, F6), -139.9 (1F, $^4\text{J}_{\text{FF}}$ 22.4, F4); m/z (ES^+) 204 (100%, $[\text{M}+\text{H}]^+$).

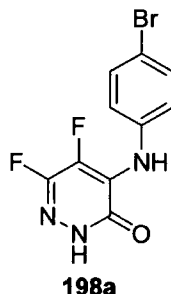
4-(4-Methoxyphenylamino)-5,6-difluoropyridazin-3(2H)-one 196a



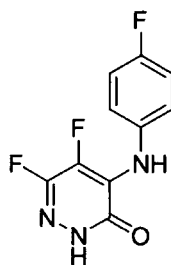
p-Anisidine (0.16443g, 1.33mmol) was mixed with 4,5,6-trifluoropyridazin-3(2H)-one (100mg, 0.666mmol) in a Radleys Greenhouse tube under nitrogen. Acetonitrile (5ml) was added and the mixture stirred at room temperature for 48 hours. After this period the solvent was evaporated, and the residue dissolved in dichloromethane (10ml). Water (10ml) was added and the organic layer separated on a hydrophobic frit. The aqueous layer was then extracted with further portions of dichloromethane ($2 \times 10\text{ml}$). The combined organic extracts were dried (MgSO_4), filtered and evaporated on a blowdown evaporator, followed by purification by flash column chromatography (elutant cyclohexane : ethyl acetate 4:1 to 2:1 gradient over 18 minutes) to yield 4-(4-methoxyphenylamino)-5,6-difluoropyridazin-3(2H)-one **196a** (0.102g, 61%) as a white solid; mp 148 – 149°C (Found $[\text{MH}]^+$ 254.07362. $\text{C}_{11}\text{H}_9\text{F}_2\text{N}_3\text{O}_2$ requires $[\text{MH}]^+$ 254.07356); δ_{H} (400MHz, CD_3OD) 3.79 (3H, s, OCH_3), 6.89 (2H, d, $^3\text{J}_{\text{HH}}$ 8.9, $^4\text{J}_{\text{HH}}$ 3.3, C3'(H)), 7.17 (2H, dd, $^3\text{J}_{\text{HH}}$ 8.9, $^4\text{J}_{\text{HH}}$ 3.0, C2'(H)); δ_{F} (376MHz, CD_3OD) -105.2 (1F, d, $^3\text{J}_{\text{FF}}$ 26.6, F6), -147.9 (1F, d, $^3\text{J}_{\text{FF}}$ 26.6, F5); m/z (ES^+) 254 (100%, $[\text{M}+\text{H}]^+$).

4-(*p*-Tolylamino)-5,6-difluoropyridazin-3(2*H*)-one 197a

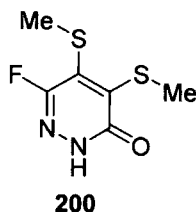
p-Toluidine (0.143g, 1.33mmol) was mixed with 4,5,6-trifluoropyridazin-3(2*H*)-one (100mg, 0.666mmol) in a Radleys Greenhouse tube under nitrogen. Acetonitrile (5ml) was added and the mixture stirred at room temperature for 48 hours. After this period the solvent was evaporated, and the residue dissolved in dichloromethane (10ml). Water (10ml) was added and the organic layer separated on a hydrophobic frit. The aqueous layer was then extracted with further portions of dichloromethane (2 × 10ml). The combined organic extracts were dried (MgSO₄), filtered and evaporated on a blowdown evaporator, followed by purification by flash column chromatography (elutant cyclohexane : ethyl acetate 4:1 to 2:1 gradient over 18 minutes) to yield 4-(*p*-tolylamino)-5,6-difluoropyridazin-3(2*H*)-one **197a** (0.088g, 56%) as a white solid; mp 157 – 158°C (Found [MH]⁺ 238.07866. C₁₁H₉F₂N₃O requires [MH]⁺ 238.07864); ν_{max} / cm⁻¹ 1051, 1218, 1269, 1450, 1512, 1571, 1634 (CO amide), 2929 (br, NH); δ_H (400MHz, CDCl₃) 2.37 (3H, s, Ar-CH₃), 7.05 (2H, dd, ³J_{HH} 8.3, ⁶J_{HF} 3.3, C2'(H)), 7.17 (2H, d, ³J_{HH} 8.3, C3'(H)), 7.25 (1H, br s, NHAr), 11.19 (1H, br s, ring NH); δ_C (100MHz, CDCl₃) 20.9 (s, ArCH₃), 122.5 (d, ⁴J_{CF} 4.0, C1'), 128.8 (d, ²J_{CF} 8.8, C4), 129.5 (s, ArC), 131.9 (dd, ¹J_{CF} 267.6, ²J_{CF} 32.8, C5), 134.9 (s, ArC), 135.5 (s, ArC), 148.9 (dd, ¹J_{CF} 232.5, ²J_{CF} 17.6, C6), 160.0 (d, ³J_{CF} 10.4, C3); δ_F (376MHz, CDCl₃) -105.1 (1F, d, ³J_{FF} 26.4, F6), -142.4 (1F, d, ³J_{FF} 26.4, F5); *m/z* (ES⁻) 236 (100%, [M-H]).

4-(4-Bromophenylamino)-5,6-difluoropyridazin-3(2H)-one 198a

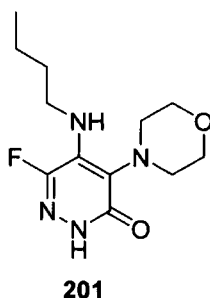
4-Bromoaniline (3.43g, 20.0mmol) was mixed with 4,5,6-trifluoropyridazin-3(2H)-one (1.50g, 10.0mmol) in a round bottom flask under nitrogen. Acetonitrile (50ml) was added and the mixture heated to reflux for 16 hours. After this period the solvent was evaporated, and the residue dissolved in dichloromethane (50ml). Water (50ml) was added and the organic layer separated. The aqueous layer was then extracted with further portions of dichloromethane (3 × 50ml). The combined organic extracts were dried (MgSO₄), filtered and evaporated *in vacuo*, followed by purification by recrystallisation from acetonitrile to yield 4-(4-bromophenylamino)-5,6-difluoropyridazin-3(2H)-one **198a**; (1.27g, 42%) as a white solid; mp 162 – 164°C (Found [MH, ⁷⁹Br]⁺ 301.97365. C₁₀H₆F₂N₃O requires [MH, ⁷⁹Br]⁺ 301.97351); ν_{max} / cm⁻¹ 1025, 1095, 1217, 1455, 1489, 1584, 1637 (CO amide), 3002 (br, NH); δ_H (400MHz, CDCl₃) 7.02 (2H, dd, ³J_{HH} 8.3, ⁶J_{HF} 4.0, C2'(H)), 7.24 (1H, br s, NHAr) 7.44 (2H, d, ³J_{HH} 8.3, C3'(H)); δ_C (100MHz, CDCl₃) 121.6 (s, ArC), 127.2 (d, ⁴J_{CF} 4.8, C1'), 131.8 (d, ²J_{CF} 8.8, C4), 135.4 (s, ArC), 136.2 (dd, ¹J_{CF} 268.4, ²J_{CF} 33.6, C5), 140.7 (s, ArC), 152.0 (dd, ¹J_{CF} 231.7, ²J_{CF} 17.6, C6), 163.2 (d, ³J_{CF} 9.6, C3); δ_F (376MHz, CDCl₃) -104.6 (1F, d, ³J_{FF} 26.9, F6), -142.4 (1F, d, ³J_{FF} 26.9, F5); *m/z* (ES⁺) 304 (100%, [M+H]⁺, ⁸¹Br), 302 (96, [M+H]⁺, ⁷⁹Br).

4-(4-Fluorophenylamino)-5,6-difluoropyridazin-3(2H)-one 199a**199a**

4-Fluoroaniline (0.74g, 6.66mmol) was mixed with 4,5,6-trifluoropyridazin-3(2H)-one (0.50g, 3.33mmol) in a round bottom flask under nitrogen. Acetonitrile (50ml) was added and the mixture heated to reflux for 16 hours. After this period the solvent was evaporated, and the residue dissolved in dichloromethane (25ml). Water (25ml) was added and the organic layer separated. The aqueous layer was then extracted with further portions of dichloromethane ($3 \times 25\text{ml}$). The combined organic extracts were dried (MgSO_4), filtered and evaporated *in vacuo*, followed by purification by recrystallisation from acetonitrile to yield 4-(4-fluorophenylamino)-5,6-difluoropyridazin-3(2H)-one **199a**; (0.42g, 52%) as a white solid; mp $162 - 163^\circ\text{C}$ (Found C, 49.7; H, 2.6; N, 17.4. $\text{C}_8\text{H}_9\text{N}_3\text{F}_2\text{O}_2$ requires C, 49.8; H, 2.5; N, 17.4%); $\nu_{\text{max}} / \text{cm}^{-1}$ 1209, 1453, 1511, 1585, 1639 (CO amide), 3200 (br, NH); δ_{H} (500MHz, DMSO-d_6) 7.12 (2H, t, $^3J_{\text{HH}}$ 8.7, C2'(H)), 7.20 (2H, m, C3'(H)), 8.80 (1H, br s, NHAr), 12.63 (1H, br s, ring NH); δ_{C} (125MHz, DMSO-d_6) 115.6 (d, $^2J_{\text{CF}}$ 22.5, C3'), 124.7 (dd, $^3J_{\text{CF}}$ 8.3, $^4J_{\text{CF}}$ 3.9, C4), 129.4 (d, $^3J_{\text{CF}}$ 8.9, C2'), 132.6 (dd, $^1J_{\text{CF}}$ 263.9, $^2J_{\text{CF}}$ 33.7, C5), 136.0 (dd, $^3J_{\text{CF}}$ 2.9, $^4J_{\text{CF}}$ 1.6, C1'), 148.2 (dd, $^1J_{\text{CF}}$ 224.8, $^2J_{\text{CF}}$ 17.4, C6), 159.5 (d, $^1J_{\text{CF}}$ 240.1, C4'), 159.8 (d, $^3J_{\text{CF}}$ 9.1, C3); δ_{F} (376MHz, CDCl_3) -103.3 (1F, d, $^3J_{\text{FF}}$ 29.7, F6), -114.3 (1F, m, F4'), -139.7 (1F, d, $^3J_{\text{FF}}$ 29.7, F5); m/z (ES^+) 305 (100%, $[\text{M}+\text{MeCN}+\text{Na}]^+$), 283 (96, $[\text{M}+\text{MeCN}+\text{H}]^+$), 242 (4, $[\text{M}+\text{H}]^+$).

6-Fluoro-4,5-bis(methylthio)pyridazin-3(2H)-one 200

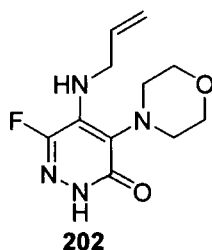
A clean, dry round bottomed flask was charged with 4,5,6-Trifluoropyridazin-3(2H)-one (0.50g, 3.33mmol) and sodium thiomethoxide (0.47g, 6.66mmol), before being purged and filled with argon. The solids were dissolved in acetonitrile (20ml), and the mixture stirred at room temperature for 6 hours. After this period water (20ml) was added followed by dichloromethane (20ml), and the organic layer separated. The aqueous layer was then extracted with further portions of dichloromethane (2 × 20ml), and the combined organic extracts were dried (MgSO₄), filtered and evaporated under vacuum to yield a crude yellow product (0.59g). This was purified by recrystallisation from acetonitrile to yield 6-fluoro-4,5-bis(methylthio)pyridazin-3(2H)-one **200** (0.38g, 55%) as yellow crystals; mp 138 – 140°C (Found C, 35.0; H, 3.4; N, 13.7. C₆H₇N₂FOS₂ requires C, 34.9; H, 3.4; N, 13.6%); ν_{\max} / cm⁻¹ 1136, 1356, 1435, 1628 (CO amide), 2833 (br, NH); δ_{H} (500MHz, CDCl₃) 2.61 (3H, d, ⁵J_{HF} 4.0, C5-SCH₃), 3.81 (3H, s, C4-SCH₃), 11.88 (1H, br s, ring NH); δ_{C} (125MHz, CDCl₃) 17.0 (s, C4-SCH₃), 17.7 (d, ⁴J_{CF} 11.6, C5-SCH₃), 134.7 (d, ²J_{CF} 34.6, C5), 142.8 (d, ³J_{CF} 6.5, C4), 152.4 (d, ¹J_{CF} 234.3, C6), 159.8 (s, C3); δ_{F} (376MHz, CDCl₃) -89.5 (1F, s, F6); m/z (EI⁺) 206 (6%, [M]⁺), 291 (52, [M-Me]⁺), 87 (100), 45 (78). Crystals suitable for X-ray diffraction grown by slow evaporation of acetonitrile.

5-(Butylamino)-6-fluoro-4-morpholinopyridazin-3(2H)-one 201

5,6-Difluoro-4-morpholinopyridazin-3(2H)-one (200mg, 0.921mmol) was mixed with acetonitrile (3ml) and *n*-butylamine (0.135g, 1.84mmol) in a 2-5 ml microwave vial, which was sealed and the mixture irradiated at 150°C for 30 minutes. After this period the

solvent was evaporated, and the residue dissolved in dichloromethane (10ml). Water (10ml) was added and the organic layer separated on a hydrophobic frit. The aqueous layer was then extracted with further portions of dichloromethane ($2 \times 10\text{ml}$). The combined organic extracts were dried (MgSO_4), filtered and evaporated on a blowdown evaporator, followed by recrystallisation from acetonitrile to yield *5-(butylamino)-6-fluoro-4-morpholinopyridazin-3(2H)-one* **201** (0.136g, 55%) as a white solid; mp $127 - 128^\circ\text{C}$ (Found $[\text{MH}]^+$ 271.15633. $\text{C}_{15}\text{H}_{17}\text{N}_4\text{FO}_2$ requires $[\text{MH}]^+$ 271.15648); $\nu_{\text{max}} / \text{cm}^{-1}$ 1105, 1166, 1260, 1370, 1457, 1557, 1610 (CO amide), 2851 (br, NH); δ_{H} (400MHz, CDCl_3) 0.97 (3H, t, $^3J_{\text{HH}}$ 7.5, $\text{NHCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 1.41 (2H, sextet, $^3J_{\text{HH}}$ 7.5, $\text{NHCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 1.58 (2H, pent, $^3J_{\text{HH}}$ 7.5, $\text{NHCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 3.14 (4H, t, $^3J_{\text{HH}}$ 5.9, $\text{C2}'(\text{H})$), 3.45 (2H, qd, $^3J_{\text{HH}}$ 6.5, $^5J_{\text{HF}}$ 3.5, $\text{NHCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 3.77 (4H, t, $^3J_{\text{HH}}$ 5.9, $\text{C3}'(\text{H})$), 5.53 (1H, br t, $^3J_{\text{HH}}$ 6.5, NHBu), 11.81 (1H, br s, ring NH); δ_{C} (100MHz, CDCl_3) 13.7 (s, $\text{NHCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 19.8 (s, $\text{NHCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 33.0 (d, $^5J_{\text{CF}}$ 1.6, $\text{NHCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 44.2 (d, $^4J_{\text{CF}}$ 8.8, $\text{NHCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 48.6 (s, $\text{C2}'$), 67.7 (s, $\text{C3}'$), 125.1 (d, $^3J_{\text{CF}}$ 11.2, C4), 138.7 (d, $^2J_{\text{CF}}$ 24.8, C5), 147.5 (d, $^1J_{\text{CF}}$ 234.1, C6), 161.5 (m, C3); δ_{F} (376MHz, CDCl_3) -99.2 (1F, s); m/z (ES^+) 271 (100%, $[\text{M}+\text{H}]^+$).

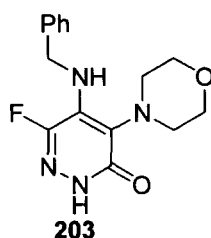
5-(Allylamino)-6-fluoro-4-morpholinopyridazin-3(2H)-one **202**



5,6-Difluoro-4-morpholinopyridazin-3(2H)-one (200mg, 0.921mmol) was mixed with acetonitrile (3ml) and allylamine (0.14ml, 1.84mmol) in a 2-5 ml microwave vial, which was sealed and the mixture irradiated at 150°C for minutes. After this period the solvent was evaporated, and the residue dissolved in dichloromethane (10ml). Water (10ml) was added and the organic layer separated on a hydrophobic frit. The aqueous layer was then extracted with further portions of dichloromethane ($2 \times 10\text{ml}$). The combined organic extracts were dried (MgSO_4), filtered and evaporated on a blowdown evaporator, followed by recrystallisation from acetonitrile to yield *5-(allylamino)-6-fluoro-4-morpholinopyridazin-3(2H)-one* **202** (0.124g, 56%) as a white solid; mp $159 - 160^\circ\text{C}$

(Found $[\text{MH}]^+$ 255.12506. $\text{C}_{11}\text{H}_{15}\text{FN}_4\text{O}_2$ requires $[\text{MH}]^+$ 255.12518); ν_{max} / cm^{-1} 1106, 1166, 1259, 1370, 1491, 1555, 1608 (CO amide), 2802 (br, NH); δ_{H} (400MHz, CDCl_3) 3.15 (4H, t, $^3J_{\text{HH}}$ 4.7, $\text{C2}'(\text{H})$), 3.77 (4H, t, $^3J_{\text{HH}}$ 4.7, $\text{C3}'(\text{H})$), 4.09 (2H, dt, $^3J_{\text{HH}}$ 6.5, $^5J_{\text{HF}}$ 2.0, $\text{NHCH}_2\text{CH}=\text{CH}_2$), 5.20 (2H, m, $\text{NHCH}_2\text{CH}=\text{CH}_2$), 5.63 (1H, t, $^3J_{\text{HH}}$ 6.3, $\text{NHCH}_2\text{CH}=\text{CH}_2$), 5.92 (1H, m, $\text{NHCH}_2\text{CH}=\text{CH}_2$), 11.54 (1H, br s, ring NH); δ_{C} (100MHz, CDCl_3) 46.5 (d, $^4J_{\text{CF}}$ 9.6, $\text{NHCH}_2\text{CH}=\text{CH}_2$), 48.6 (s, $\text{C2}'$), 67.6 (s, $\text{C3}'$), 116.4 (s), 125.8 (d, $^3J_{\text{CF}}$ 10.4, C4), 134.8 (s), 138.4 (d, $^2J_{\text{CF}}$ 24.8, C5), 147.5 (d, $^1J_{\text{CF}}$ 234.1, C6), 161.5 (s, C3); δ_{F} (376MHz, CDCl_3) -98.9 (1F, s); m/z (ES^+) 509 (100%, $[\text{2M}+\text{H}]^+$), 255 (53, $[\text{M}+\text{H}]^+$).

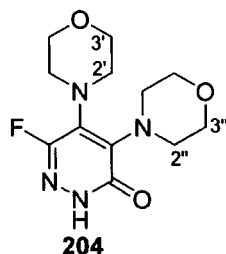
5-(Benzylamino)-6-fluoro-4-morpholinopyridazin-3(2H)-one 203



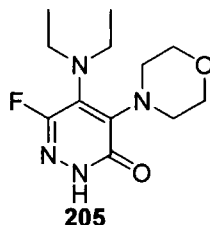
5,6-Difluoro-4-morpholinopyridazin-3(2H)-one (0.25g, 1.15mmol) was dissolved in dry acetonitrile (40ml) under argon with stirring. Benzylamine (0.25ml, 2.30mmol) was added dropwise, and the mixture heated to reflux for 72 hours, after which ^{19}F NMR indicated complete conversion to products. Water (25ml) and dichloromethane (25ml) were added, and the layers separated. The aqueous layer was then extracted with further portions of dichloromethane ($2 \times 25\text{ml}$), before the combined organic extracts were dried (MgSO_4) and filtered. The solvent was removed *in vacuo* to yield a crude yellow solid (0.17g). This was recrystallised from acetonitrile to yield 5-(benzylamino)-6-fluoro-4-morpholinopyridazin-3(2H)-one **203** (0.22g, 62%) as a cream solid; mp 199 – 201°C (Found C, 58.8; H, 5.7; N, 18.2. $\text{C}_{15}\text{H}_{17}\text{N}_4\text{FO}_2$ requires C, 59.2; H, 5.6; N, 18.4%); ν_{max} / cm^{-1} 1012, 1115, 1212, 1258, 1443, 1460, 1630 (CO amide), 2878 (br, NH); δ_{H} (500MHz, CDCl_3) 1.69 (1H, br s, OH hydroxy-pyridazine tautomer), 3.12 (4H, br t, $^3J_{\text{HH}}$ 4.7, $\text{C2}'(\text{H})$), 3.72 (4H, t, $^3J_{\text{HH}}$ 4.7, $\text{C3}'(\text{H})$), 4.66 (2H, dd, $^3J_{\text{HH}}$ 6.4, $^5J_{\text{HF}}$ 1.8, CH_2Ph), 5.82 (1H, t, $^3J_{\text{HH}}$ 6.4, NHBn), 7.26 (2H, d, $^3J_{\text{HH}}$ 7.3, $\text{C2}'(\text{H})$), 7.34 (1H, d, $^3J_{\text{HH}}$ 7.3, $\text{C4}'(\text{H})$), 7.39 (2H, t, $^3J_{\text{HH}}$ 7.3, $\text{C3}'(\text{H})$), 11.05 (1H, br s, ring NH); δ_{C} (125MHz, CDCl_3) 48.8 (d, $^4J_{\text{CF}}$ 9.0, CH_2Ph), 48.9 (s), 67.8 (s), 126.7 (d, $^5J_{\text{CF}}$ 10.4, $\text{Ar}(\text{C1}')$), 127.2 (s, ArC), 128.2 (s, ArC), 129.3 (s,

ArC), 138.8 (d, $^2J_{CF}$ 15.2, C5), 138.9 (d, $^3J_{CF}$ 9.0, C4), 147.9 (d, $^1J_{CF}$ 234.0, C6), 161.5 (s, C3); δ_F (376MHz, $CDCl_3$) -98.2 (1F, s); m/z (ES^+) 305 (100%, $[M+H]^+$).

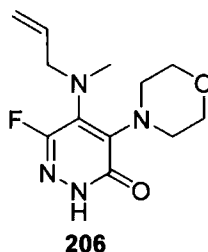
6-Fluoro-4,5-dimorpholinopyridazin-3(2H)-one 204



5,6-Difluoro-4-morpholinopyridazin-3(2H)-one (200mg, 0.921mmol) was mixed with acetonitrile (3ml) and morpholine (0.160g, 1.84mmol) in a 2-5 ml microwave vial, which was sealed and the mixture irradiated at 150°C for 30 minutes. After this period the solvent was evaporated, and the residue dissolved in dichloromethane (10ml). Water (10ml) was added and the organic layer separated on a hydrophobic frit. The aqueous layer was then extracted with further portions of dichloromethane (2 × 10ml). The combined organic extracts were dried ($MgSO_4$), filtered and evaporated on a blowdown evaporator to yield 6-fluoro-4,5-dimorpholinopyridazin-3(2H)-one **204** (0.141g, 54%) as a white solid; mp 163 – 164°C (Found $[MH]^+$ 285.13570. $C_{12}H_{17}FN_4O_3$ requires $[MH]^+$ 285.13575); ν_{max} / cm^{-1} 1026, 1118, 1190, 1241, 1268, 1397, 1415, 1514, 1619 (CO amide); δ_H (400MHz, $CDCl_3$) 3.14 (4H, t, $^3J_{HH}$ 4.0, C2'(H)), 3.48 (4H, t, $^3J_{HH}$ 4.8, C2''(H)), 3.79 (8H, m, C3'(H) + C3''(H)), 11.47 (1H, br s, ring NH); δ_C (100MHz, $CDCl_3$) 49.9 (s, C2''), 50.3 (dd, $^4J_{CF}$ 4.8, $^5J_{CF}$ 1.9, C2'), 67.0 (s, C3'), 67.5 (s, C3''), 129.9 (d, $^2J_{CF}$ 27.2, C5), 141.4 (d, $^3J_{CF}$ 11.2, C4), 154.3 (d, $^1J_{CF}$ 237.3, C6), 161.7 (s, C3); δ_F (376MHz, $CDCl_3$) -94.2 (1F, s); m/z (ES^+) 285 (100%, $[M+H]^+$).

5-(Diethylamino)-6-fluoro-4-morpholinopyridazin-3(2H)-one 205

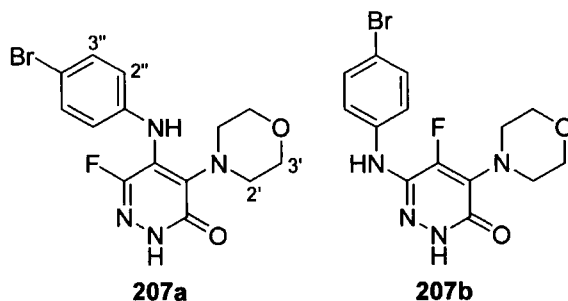
5,6-Difluoro-4-morpholinopyridazin-3(2H)-one (200mg, 0.921mmol) was mixed with acetonitrile (3ml) and diethylamine (0.19ml, 1.84mmol) in a 2-5 ml microwave vial, which was sealed and the mixture irradiated at 150°C for minutes. After this period the solvent was evaporated, and the residue dissolved in dichloromethane (10ml). Water (10ml) was added and the organic layer separated on a hydrophobic frit. The aqueous layer was then extracted with further portions of dichloromethane (2 × 10ml). The combined organic extracts were dried (MgSO₄), filtered and evaporated on a blowdown evaporator to yield a crude yellow solid. This was then purified by flash column chromatography (elutant cyclohexane : ethyl acetate) to yield *5-(diethylamino)-6-fluoro-4-morpholinopyridazin-3(2H)-one 205* (0.0613g, 25%) as a white solid; mp 105 – 107°C (Found [MH]⁺ 271.15643. C₁₂H₁₉FN₄O₂ requires [MH]⁺ 271.15648); δ_H (400MHz, CDCl₃) 1.05 (6H, t, ³J_{HH} 6.7, NCH₂CH₃), 3.11 (4H, q, ³J_{HH} 6.7, NCH₂CH₃), 3.46 (4H, m, C2'(H)), 3.80 (4H, m, C3'(H)), 11.56 (1H, br s, ring NH); δ_C (100MHz, CDCl₃) 13.1 (s, NCH₂CH₃), 46.1 (d, ⁴J_{CF} 4.8, NCH₂CH₃), 49.2 (s, C2'), 67.5 (s, C3'), 128.3 (d, ²J_{CF} 28.0, C5), 142.0 (d, ³J_{CF} 11.2, C4), 155.5 (d, ¹J_{CF} 237.3, C6), 161.3 (s, C3); δ_F (376MHz, CDCl₃) -94.6 (1F, s); *m/z* (ES⁺) 271 (100%, [M+H]⁺).

5-(N-Allyl-N-methylamino)-6-fluoro-4-morpholinopyridazin-3(2H)-one 206

5,6-Difluoro-4-morpholinopyridazin-3(2H)-one (200mg, 0.921mmol) was mixed with acetonitrile (3ml) and N-allylmethylamine (0.18ml, 1.84mmol) in a 2-5 ml microwave vial, which was sealed and the mixture irradiated at 150°C for minutes. After this period

the solvent was evaporated, and the residue dissolved in dichloromethane (10ml). Water (10ml) was added and the organic layer separated on a hydrophobic frit. The aqueous layer was then extracted with further portions of dichloromethane ($2 \times 10\text{ml}$). The combined organic extracts were dried (MgSO_4), filtered and evaporated on a blowdown evaporator to yield 5-(*N*-allyl-*N*-methlamino)-6-fluoro-4-morpholinopyridazin-3(2*H*)-one **206** (0.100g, 43%) as a white solid; mp $86 - 87^\circ\text{C}$ (Found $[\text{MH}]^+$ 269.14070. $\text{C}_{12}\text{H}_{17}\text{FN}_4\text{O}_2$ requires $[\text{MH}]^+$ 269.14083); $\nu_{\text{max}} / \text{cm}^{-1}$ 992, 1113, 1232, 1535, 1654 (CO amide), 2859 (br, NH); δ_{H} (400MHz, CDCl_3) 2.79 (3H, d, $^4J_{\text{HF}}$ 2.8, NMe), 3.45 (4H, t, $^3J_{\text{HH}}$ 4.6, C2'(H)), 3.64 (2H, d, $^3J_{\text{HH}}$ 6.3, $\text{NCH}_2\text{CH}=\text{CH}_2$), 3.80 (4H, t, $^3J_{\text{HH}}$ 4.6, C3'(H)), 5.18 (2H, m, $\text{NCH}_2\text{CH}=\text{CH}_2$), 5.79 (1H, m, $\text{NCH}_2\text{CH}=\text{CH}_2$), 11.27 (1H, br s, ring NH); δ_{C} (100MHz, CDCl_3) 39.8 (d, $^4J_{\text{CF}}$ 4.8, NMe), 46.3 (s, C2'), 57.4 (d, $^4J_{\text{CF}}$ 4.0, $\text{NCH}_2\text{CH}=\text{CH}_2$), 67.5 (s, C3'), 118.5 (s, $\text{NCH}_2\text{CH}=\text{CH}_2$), 130.4, (d, $^2J_{\text{CF}}$ 28.0, C5), 133.9 (s, $\text{NCH}_2\text{CH}=\text{CH}_2$), 140.7 (d, $^3J_{\text{CF}}$ 10.4, C4), 154.6 (d, $^1J_{\text{CF}}$ 236.5, C6), 161.6 (s, C3); δ_{F} (376MHz, CDCl_3) -94.5 (1F, s); m/z (ES^+) 269 (100%, $[\text{M}+\text{H}]^+$).

5-(4-Bromophenylamino)-6-fluoro-4-morpholinopyridazin-3(2*H*)-one **207a** and 6-(4-bromophenylamino)-5-fluoro-4-morpholinopyridazin-3(2*H*)-one **207b**

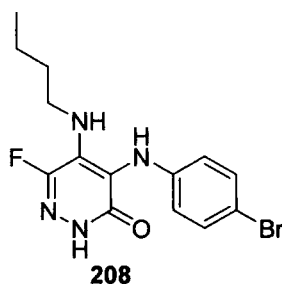


4-Bromoaniline (0.396g, 2.30mmol) was mixed with sodium hydride (0.09g, 2.30mmol, 60% dispersion in mineral oil) and THF (10ml) in a Radleys Carousel tube under nitrogen with stirring. 5,6-difluoro-4-morpholinopyridazin-3(2*H*)-one (50mg, 0.230mmol) was added and the mixture heated to reflux for 64 hours. After this period the solvent was evaporated, and the residue dissolved in dichloromethane (10ml). Water (10ml) was added and the organic layer separated on a hydrophobic frit. The aqueous layer was then extracted with further portions of dichloromethane ($2 \times 10\text{ml}$). The combined organic extracts were dried (MgSO_4), filtered and evaporated on a blowdown evaporator, followed by purification by mass directed automated purification to yield 5-(4-

bromophenylamino)-6-fluoro-4-morpholinopyridazin-3(2*H*)-one **207a** (0.0091g, 11%) as a white solid; mp 178 – 179°C (Found $[\text{}^{79}\text{Br}, \text{MH}]^+$ 369.03521; $\text{C}_{14}\text{H}_{14}\text{BrFN}_4\text{O}_2$ requires $[\text{}^{79}\text{Br}, \text{MH}]^+$ 369.03569); δ_{H} (400MHz, CDCl_3) 3.27 (4H, t, $^3J_{\text{HH}}$ 4.8, C2'(H)), 3.60 (4H, t, $^3J_{\text{HH}}$ 4.8, C3'(H)), 6.18 (1H, br s, NHArBr), 6.78 (2H, d, $^3J_{\text{HH}}$ 8.5, C2''(H)), 7.43 (2H, d, $^3J_{\text{HH}}$ 8.5, C3''(H)), 10.25 (1H, br s, ring NH); δ_{C} (100MHz, CDCl_3) 48.3 (s, C2'), 67.2 (s, C3'), 116.2 (s), 121.1 (s), 124.8 (d, $^2J_{\text{CF}}$ 27.2, C5), 132.0 (s), 137.4 (d, $^3J_{\text{CF}}$ 7.2, C4), 138.5 (s), 149.9 (d, $^1J_{\text{CF}}$ 232.5, C6), 160.5 (s, C3); δ_{F} (376MHz, CDCl_3) -97.9 (1F, s); m/z (ES^+) 371 (100%, $[\text{}^{81}\text{Br}, \text{M}+\text{H}]^+$), 369 (97, $[\text{}^{79}\text{Br}, \text{M}+\text{H}]^+$).

A small sample of the minor isomer 6-(4-bromophenylamino)-5-fluoro-4-morpholinopyridazin-3(2*H*)-one **207b** was also obtained; (0.0059g, 7%) as a white solid; δ_{F} (376MHz, CDCl_3) -143.6 (1F, s); m/z (ES^+) 371 (98%, $[\text{}^{81}\text{Br}, \text{M}+\text{H}]^+$), 369 (100, $[\text{}^{79}\text{Br}, \text{M}+\text{H}]^+$).

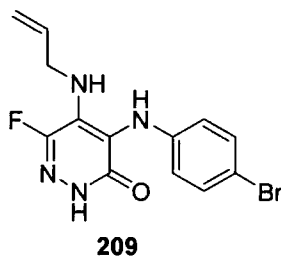
4-(4-Bromophenylamino)-5-(butylamino)-6-fluoropyridazin-3(2*H*)-one **208**



4-(4-Bromophenylamino)-5,6-difluoropyridazin-3(2*H*)-one (100mg, 0.331mmol) was added to a 2-5ml microwave vial, along with acetonitrile (3ml) and butylamine (0.0818ml, 0.828mmol). The vial was sealed, and the mixture irradiated at 150°C for 30 minutes. After this period the solvent was evaporated in a blowdown evaporator, and the crude residue dissolved in dichloromethane (10ml). Water (10ml) was added and the mixture separated on a hydrophobic frit. The aqueous layer was washed with further portions of dichloromethane ($2 \times 10\text{ml}$). The combined organic extracts were then dried over MgSO_4 , filtered and evaporated to yield a crude yellow solid. This was then purified by elution through an SCX-2 column with methanol. This yielded 4-(4-bromophenylamino)-5-(butylamino)-6-fluoropyridazin-3(2*H*)-one **208** (0.0987g, 90%) as a yellow solid; mp 150 – 152°C (Found $[\text{}^{79}\text{Br}, \text{MH}]^+$ 355.05597. $\text{C}_{14}\text{H}_{16}\text{BrFN}_4\text{O}$ requires $[\text{}^{79}\text{Br}, \text{MH}]^+$ 355.05643); δ_{H} (400MHz, CDCl_3) 0.82 (3H, t, $^3J_{\text{HH}}$ 7.3, $\text{NHCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$)

1.19 (2H, sextet, $^3J_{\text{HH}}$ 7.3, $\text{NHCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 1.35 (2H, pent, $^3J_{\text{HH}}$ 7.3, $\text{NHCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 3.12 (2H, q, $^3J_{\text{HH}}$ 6.0, $\text{NHCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 3.91 (1H, br t, $^3J_{\text{HH}}$ 6.0, NHBU), 6.58 (2H, d, $^3J_{\text{HH}}$ 8.8, $\text{C2}'(\text{H})$), 6.84 (1H, br s, NHAr), 7.31 (2H, d, $^3J_{\text{HH}}$ 8.8, $\text{C3}'(\text{H})$), 12.00 (1H, br s, ring NH); δ_{C} (100MHz, CDCl_3) 13.5 (s, $\text{NHCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 19.6 (s, $\text{NHCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 32.7 (s, $\text{NHCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 43.8 (d, $^4J_{\text{CF}}$ 4.8, $\text{NHCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 113.44 (s, ArC), 118.5 (s, ArC), 119.2 (d, $^3J_{\text{CF}}$ 10.4, C4), 129.5 (d, $^2J_{\text{CF}}$ 27.2, C5), 131.7 (s, ArC), 140.4 (s, ArC), 148.5 (d, $^1J_{\text{CF}}$ 230.9, C6), 161.0 (s, C3); δ_{F} (376MHz, CDCl_3) -99.9 (1F, s, F6); m/z (ES^+) 355 (100%, $[\text{Br}, \text{M}+\text{H}]^+$), 353 (99, $[\text{Br}, \text{M}+\text{H}]^+$).

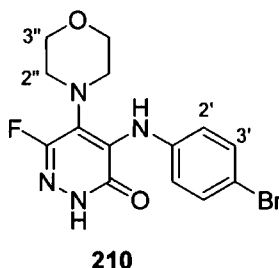
4-(4-Bromophenylamino)-5-(allylamino)-6-fluoropyridazin-3(2H)-one **209**



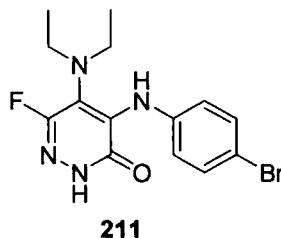
4-(4-Bromophenylamino)-5,6-difluoropyridazin-3(2H)-one (100mg, 0.331mmol) was added to a 2-5ml microwave vial, along with acetonitrile (3ml) and allylamine (0.0621ml, 0.828mmol). The vial was sealed, and the mixture irradiated at 150°C for 30 minutes. After this period the solvent was evaporated in a blowdown evaporator, and the crude residue dissolved in dichloromethane (10ml). Water (10ml) was added and the mixture separated on a hydrophobic frit. The aqueous layer was washed with further portions of dichloromethane (2 × 10ml). The combined organic extracts were then dried over MgSO_4 , filtered and evaporated to yield a crude yellow solid. This was then purified by flash column chromatography (Elutant ethyl acetate : hexane – gradient 10% to 33% EtOAc over 20 minutes. This yielded *4-(4-bromophenylamino)-5-(allylamino)-6-fluoropyridazin-3(2H)-one* **209** (0.0502g, 45%) as a white solid; mp 167 – 168°C (Found $[\text{Br}, \text{MH}]^+$ 339.02469. $\text{C}_{13}\text{H}_{12}\text{BrFN}_4\text{O}$ requires $[\text{Br}, \text{MH}]^+$ 339.02513); ν_{max} / cm^{-1} 1269, 1303, 1435, 1618 (CO amide), 2813 (br, NH); δ_{H} (400MHz, CDCl_3) 3.67 (2H, td, $^3J_{\text{HH}}$ 6.2, $^5J_{\text{HF}}$ 1.5, $\text{NHCH}_2\text{CH}=\text{CH}_2$), 3.94 (1H, dt, $^3J_{\text{HH}}$ 6.2, $^4J_{\text{HF}}$ 2.8, NHAllyl), 5.06 (1H, m, $\text{NHCH}_2\text{CH}=\text{CH}_2$), 5.09 (1H, m, $\text{NHCH}_2\text{CH}=\text{CH}_2$), 5.66 (1H, m, $\text{NHCH}_2\text{CH}=\text{CH}_2$), 6.64 (2H, d, $^3J_{\text{HH}}$ 8.8, $\text{C2}'(\text{H})$), 6.71 (1H, br s, NHAr), 7.37 (2H, d, $^3J_{\text{HH}}$ 8.8, $\text{C3}'(\text{H})$), 11.17 (1H,

br s, ring NH); δ_C (100MHz, $CDCl_3$) 46.2 (d, $^4J_{CF}$ 4.8, $NHCH_2CH=CH_2$), 114.2 (s), 117.2 (s), 119.2 (s), 120.6 (d, $^3J_{CF}$ 9.6, C4), 127.5 (d, $^2J_{CF}$ 27.2, C5), 131.9 (s), 134.2 (s), 139.7 (s), 148.7 (d, $^1J_{CF}$ 230.9, C6), 160.4 (s, C3); δ_F (376MHz, $CDCl_3$) -99.8 (1F, s, F6); m/z (ES^+) 341 (100%, [^{81}Br , $M+H$] $^+$), 339 (96, [^{79}Br , $M+H$] $^+$).

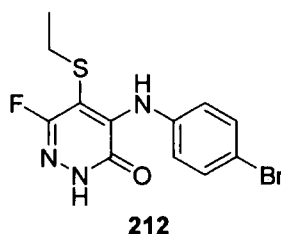
4-(4-Bromophenylamino)-5-(diethylamino)-6-fluoropyridazin-3(2H)-one 210



4-(4-bromophenylamino)-5,6-difluoropyridazin-3(2H)-one (100mg, 0.331mmol) was added to a 2-5ml microwave vial, along with acetonitrile (3ml) and morpholine (0.0621ml, 0.828mmol). The vial was sealed, and the mixture irradiated at 150°C for 30 minutes. After this period the solvent was evaporated in a blowdown evaporator, and the crude residue dissolved in dichloromethane (10ml). Water (10ml) was added and the mixture separated on a hydrophobic frit. The aqueous layer was washed with further portions of dichloromethane (2×10 ml). The combined organic extracts were then dried over $MgSO_4$, filtered and evaporated to yield a crude yellow solid. This was then purified by mass directed automated purification, yielding 4-(4-bromophenylamino)-5-(diethylamino)-6-fluoropyridazin-3(2H)-one **210** (0.0225g, 18%) as white solid; mp 233 – 234°C (Found [^{79}Br , MH] $^+$ 369.03531; $C_{14}H_{14}BrFN_4O_2$ requires [^{79}Br , MH] $^+$ 369.03569); δ_H (400MHz, $CDCl_3$) 2.99 (4H, m, $C2''(H)$), 3.24 (4H, t, $^3J_{HH}$ 4.8, $C3''(H)$), 6.84 (2H, d, $^3J_{HH}$ 8.5, $C2'(H)$), 7.20 (1H, br s, $NHAr$), 7.45 (2H, d, $^3J_{HH}$ 8.5, $C3'(H)$), 9.68 (1H, br s, ring NH); δ_C (100MHz, $DMSO-d_6$) 47.9 (d, $^4J_{CF}$ 4.0, $C2''$), 65.5 (s, $C3''$), 113.6 (s, ArC), 122.1 (d, $^2J_{CF}$ 28.8, C5), 123.1 (s, ArC), 130.3 (s, ArC), 131.0 (d, $^3J_{CF}$ 12.7, C4), 138.5 (s), 152.5 (d, $^1J_{CF}$ 231.7, C6), 159.0 (s, C3); δ_F (376MHz, $CDCl_3$) -92.2 (1F, s, F6); m/z (ES^+) 371 (100%, [^{81}Br , $M+H$] $^+$), 369 (95, [^{79}Br , $M+H$] $^+$).

4-(4-Bromophenylamino)-5-(diethylamino)-6-fluoropyridazin-3(2H)-one 211

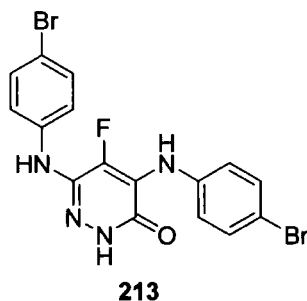
4-(4-Bromophenylamino)-5,6-difluoropyridazin-3(2H)-one (100mg, 0.331mmol) was added to a 2-5ml microwave vial, along with acetonitrile (3ml) and diethylamine (0.0856ml, 0.828mmol). The vial was sealed, and the mixture irradiated at 150°C for 30 minutes. After this period the solvent was evaporated in a blowdown evaporator, and the crude residue dissolved in dichloromethane (10ml). Water (10ml) was added and the mixture separated on a hydrophobic frit. The aqueous layer was washed with further portions of dichloromethane (2 × 10ml). The combined organic extracts were then dried over MgSO₄, filtered and evaporated to yield a crude yellow solid. This was then purified by mass directed automated purification, yielding 4-(4-bromophenylamino)-5-(diethylamino)-6-fluoropyridazin-3(2H)-one **211** (0.0179g, 15%) as a white solid; mp 110°C (decomp) (Found [⁷⁹Br, MH]⁺ 355.05609. C₁₄H₁₆BrFN₄O requires [⁷⁹Br, MH]⁺ 355.05643); δ_H (400MHz, CDCl₃) 0.97 (6H, t, ³J_{HH} 7.0, NCH₂CH₃), 2.93 (4H, q, ³J_{HH} 7.0, NCH₂CH₃), 6.79 (2H, d, ³J_{HH} 8.0, C2'(H)), 7.36 (2H, d, ³J_{HH} 8.0, C3'(H)), 10.65 (1H, br s, ring NH); δ_C (100MHz, CDCl₃) 13.2 (s, NCH₂CH₃), 44.4 (d, ⁴J_{CF} 3.8 NCH₂CH₃), 116.0 (s, ArC), 122.5 (s, ArC), 123.4 (d, ²J_{CF} 27.5, C5), 131.0 (s, ArC), 133.0 (d, ³J_{CF} 12.1, C4), 138.0 (s, ArC), 154.3 (d, ¹J_{CF} 228.5, C6), 158.2 (s, C3); δ_F (376MHz, CDCl₃) -92.8 (1F, s, F6); *m/z* (ES⁺) 357 (97%, [⁸¹Br, M+H]⁺), 355 (100, [⁷⁹Br, M+H]⁺).

4-(4-Bromophenylamino)-5-(ethylthio)-6-fluoropyridazin-3(2H)-one 212

4-(4-Bromophenylamino)-5,6-difluoropyridazin-3(2H)-one (100mg, 0.331mmol) was added to a 2-5ml microwave vial, along with acetonitrile (3ml) and sodium ethanethiolate (0.0696g, 0.828mmol). The vial was sealed, and the mixture irradiated at

120°C for 30 minutes. After this period the solvent was evaporated in a blowdown evaporator, and the crude residue dissolved in dichloromethane (10ml). Water (10ml) was added and the mixture separated on a hydrophobic frit. The aqueous layer was washed with further portions of dichloromethane (2 × 10ml). The combined organic extracts were then dried over MgSO₄, filtered and evaporated to yield a crude yellow solid. This was then purified by elution through silica with ethyl acetate, yielding *4-(4-bromophenylamino)-5-(ethylthio)-6-fluoropyridazin-3(2H)-one* **212** (0.1020g, 90%) as a yellow solid, mp 171 – 173°C (Found [⁷⁹Br, MH]⁺ 343.98589. C₁₂H₁₁BrFN₃OS requires [⁷⁹Br, MH]⁺ 343.98630); ν_{\max} / cm⁻¹ 1070, 1252, 1462, 1485, 1573, 1633 (CO amide), 3011 (br, NH); δ_{H} (400MHz, CDCl₃) 0.92 (3H, t, ³J_{HH} 7.3, SCH₂CH₃), 2.47 (2H, q, ³J_{HH} 7.3, SCH₂CH₃), 7.01 (2H, d, ³J_{HH} 8.6, C2'(H)), 7.43 (2H, d, ³J_{HH} 8.6, C3'(H)), 9.07 (1H, br s, NHAr), 12.52 (1H, br s, ring NH); δ_{C} (100MHz, CDCl₃) 13.9 (s, SCH₂CH₃), 27.3 (d, ⁴J_{CF} 3.2, SCH₂CH₃), 103.2 (d, ²J_{CF} 40.7, C5), 115.4 (s, ArC), 124.1 (s, ArC), 130.5 (s, ArC), 138.2 (s, ArC), 143.4 (d, ³J_{CF} 9.6, C4), 154.1 (d, ¹J_{CF} 221.3, C6), 156.1 (s, C3); δ_{F} (376MHz, CDCl₃) -86.2 (1F, s, F6); m/z (ES⁺) 346 (100%, [⁸¹Br, M+H]⁺), 344 (91, [⁷⁹Br, M+H]⁺).

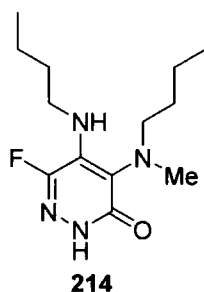
4,6-Bis(4-bromophenylamino)-5-fluoropyridazin-3(2H)-one **213**



4-Bromoaniline (0.142g, 0.828mmol) was mixed with sodium hydride (0.033g, 0.828mmol) in THF (3ml) under argon with stirring. This solution was then transferred to a 2-5ml microwave vial containing *4-(4-bromophenylamino)-5,6-difluoropyridazin-3(2H)-one* (100mg, 0.331mmol). The vial was sealed under argon, and the mixture irradiated at 120°C for 60 minutes. After this period the solvent was evaporated in a blowdown evaporator, and the crude residue dissolved in dichloromethane (10ml). Water (10ml) was added and the mixture separated on a hydrophobic frit. The aqueous layer was washed with further portions of dichloromethane (2 × 10ml). The combined organic extracts were then dried over MgSO₄, filtered and evaporated to yield a crude yellow solid. This was then

purified by mass directed automated purification, yielding *4,6-bis(4-bromophenylamino)-5-fluoropyridazin-3(2H)-one* **213** (0.0242g, 16%) as a white solid; mp 160°C (decomp) (Found $[2 \times ^{79}\text{Br}, \text{MH}]^+$ 452.93562. $\text{C}_{16}\text{H}_{11}\text{Br}_2\text{FN}_4\text{O}$ requires $[2 \times ^{79}\text{Br}, \text{MH}]^+$ 452.93564); $\nu_{\text{max}} / \text{cm}^{-1}$ 1069, 1226, 1250, 1294, 1482, 1512, 1535, 1592, 1643 (CO amide), 1666, 2887 (br, NH); δ_{H} (600MHz, DMSO- d_6) 7.05 (2H, dd, $^3J_{\text{HH}}$ 8.8, $^5J_{\text{HF}}$ 3.7), 7.42 (4H, m), 7.59 (2H, d, $^3J_{\text{HH}}$ 8.8), 8.45 (1H, br s, NHAr), 8.66 (1H, br s, NHAr), 12.34 (1H, br s, ring NH); δ_{C} (150MHz, DMSO- d_6) 112.2 (s, ArC), 114.0 (s, ArC), 120.2 (s, ArC), 122.2 (s, ArC), 122.3 (s, ArC), 124.5 (s, ArC), 130.9 (s, ArC), 131.2 (s, ArC), 137.5 (d, $^1J_{\text{CF}}$ 269.8, C5), 139.2 (d, $^2J_{\text{CF}}$ 13.7, C4), 139.6 (s, ArC), 140.2 (s, ArC), 158.1 (d, $^3J_{\text{CF}}$ 9.4, C3); δ_{F} (376MHz, CDCl_3) -138.6 (1F, s, F5); m/z (ES^+) 457 (24%, $[\text{M}+\text{H}]^+$ ($2 \times ^{81}\text{Br}$)) 455 (46, $[\text{M}+\text{H}]^+$, ($^{79}\text{Br} + ^{81}\text{Br}$)), 453 (22, $[\text{M}+\text{H}]^+$ ($2 \times ^{79}\text{Br}$)), 129 (61), 119 (100).

4-(N-Butyl-N-methylamino)-5-(butylamino)-6-fluoropyridazin-3(2H)-one **214**



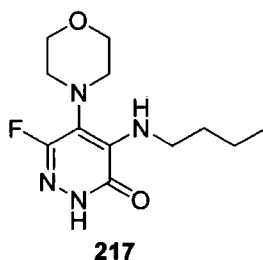
4-(N-butyl-N-methylamino)-5,6-difluoropyridazin-3(2H)-one (25mg, 0.115mmol) was dissolved in acetonitrile (0.75ml) in a 0.5 – 2ml microwave vial. After addition of butylamine (0.021g, 0.298mmol) the vial was sealed and irradiated at 150°C for 80 minutes. After this period the solvent was evaporated and the crude material dissolved in dichloromethane (10ml). Water (10ml) was added, and the organic layer separated. The aqueous portion was washed with further portions of dichloromethane, and the combined organic extracts were dried (MgSO_4), filtered and evaporated to yield a crude yellow material. This was purified by elution through an acid functionalised silica column with methanol to yield *4-(N-butyl-N-methylamino)-5-(butylamino)-6-fluoropyridazin-3(2H)-one* **214** (22.6mg, 73%) as a white solid; mp 79 – 80°C (Found $[\text{MH}]^+$ 271.19276. $\text{C}_{13}\text{H}_{23}\text{N}_4\text{FO}$ requires $[\text{MH}]^+$ 271.19287); δ_{H} (400MHz, CDCl_3) 0.90 (3H, t, $^3J_{\text{HH}}$ 7.0, $\text{NCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 0.96 (3H, t, $^3J_{\text{HH}}$ 7.3, $\text{NCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 1.35 (6H, m), 1.56 (2H, pent, $^3J_{\text{HH}}$ 7.3, $\text{NCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 2.68 (3H, s, NMe), 3.04 (2H, t, $^3J_{\text{HH}}$ 7.5,

NMeCH₂CH₂CH₂CH₃), 3.41 (2H, qd, ³J_{HH} 6.5, ⁴J_{HF} 3.0, NHCH₂CH₂CH₂CH₃), 5.54 (1H, br t, ³J_{HH} 6.5, NHBu), 11.29 (1H, br s, ring NH); δ_C (100MHz, CDCl₃) 13.7 (s, NCH₂CH₂CH₂CH₃), 13.9 (s, NCH₂CH₂CH₂CH₃), 19.8 (s, NCH₂CH₂CH₂CH₃), 20.5 (s, NCH₂CH₂CH₂CH₃), 30.8 (s, NMeCH₂CH₂CH₂CH₃), 33.2 (d, ⁵J_{CF} 1.6, NHCH₂CH₂CH₂CH₃), 39.6 (NMe), 44.1 (d, ⁴J_{CF} 9.6, NHCH₂CH₂CH₂CH₃), 53.6 (s, NMeCH₂CH₂CH₂CH₃), 126.7 (d, ³J_{CF} 11.2, C4), 139.4 (d, ²J_{CF} 24.0, C5), 147.6 (d, ¹J_{CF} 234.9, C6), 161.4 (s, C3); δ_F (376MHz, CDCl₃) -98.9 (1F, s); *m/z* (ES⁺) 271 (100%, [M+H]⁺).

Attempted Lewis acid activation of 4-benzylamino-5,6-difluoropyridazin-3(2H)-one

4-benzylamino-5,6-difluoropyridazin-3(2H)-one (0.10g, 0.422mmol) was dissolved in dry THF (10ml) under argon with stirring. Boron trifluoride diethyletherate (0.057ml, 0.463mmol) was added at 0°C and the mixture allowed to warm to room temperature. After 30 minutes diethylamine (0.087ml, 0.843mmol) was added and the mixture heated to reflux for 16 hours. After this period ¹⁹F NMR of the crude reaction mixture was measured, which showed the presence of only the starting material.

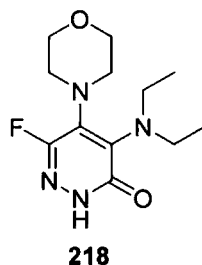
4-(Butylamino)-6-fluoro-5-morpholinopyridazin-3(2H)-one 217



4,6-Difluoro-5-morpholinopyridazin-3(2H)-one (50mg, 0.230mmol) was mixed with acetonitrile (3ml) and *n*-butylamine (0.0569ml, 0.575mmol) in a 2-5 ml microwave vial, which was sealed and the mixture irradiated at 150°C for 30 minutes. After this period the solvent was evaporated, and the residue dissolved in dichloromethane (10ml). Water (10ml) was added and the organic layer separated on a hydrophobic frit. The aqueous layer was then extracted with further portions of dichloromethane (2 × 10ml). The combined organic extracts were dried (MgSO₄), filtered and evaporated on a blowdown evaporator, followed by elution through an SCX-2 column (Biotage) with methanol to yield 4-

(butylamino)-6-fluoro-5-morpholinopyridazin-3(2H)-one **217** (0.0596g, 96%) as a white solid; mp 150 – 151°C (Found $[\text{MH}]^+$ 271.15623. $\text{C}_{15}\text{H}_{17}\text{N}_4\text{FO}_2$ requires $[\text{MH}]^+$ 271.15648); $\nu_{\text{max}} / \text{cm}^{-1}$ 1008, 1108, 1258, 1350, 1449, 1564, 1607, 1642 (CO amide), 2921 (br, NH); δ_{H} (400MHz, CDCl_3) 0.96 (3H, t, $^3J_{\text{HH}}$ 7.3, $\text{NHCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 1.43 (2H, sextet, $^3J_{\text{HH}}$ 7.3, $\text{NHCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 1.60 (2H, pent, $^3J_{\text{HH}}$ 7.3, $\text{NHCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 3.01 (4H, br t, $^3J_{\text{HH}}$ 4.4, C2'(H)), 3.77 (4H, t, $^3J_{\text{HH}}$ 4.4, C3'(H)), 3.79 (2H, t, $^3J_{\text{HH}}$ 7.3, $\text{NHCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 5.93 (1H, br s, NHBu), 11.37 (1H, br s, ring NH); δ_{C} (100MHz, CDCl_3) 13.8 (s, $\text{NHCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 20.0 (s, $\text{NHCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 32.7 (s, $\text{NHCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 44.0 (s, $\text{NHCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 50.9 (d, $^4J_{\text{CF}}$ 4.0, C2'), 66.8 (s, C3'), 114.2 (d, $^3J_{\text{CF}}$ 30.4, C4), 141.8 (d, $^2J_{\text{CF}}$ 14.4, C5), 157.4 (d, $^1J_{\text{CF}}$ 237.3, C6), 159.3 (s, C3); δ_{F} (376MHz, CDCl_3) -93.5 (1F, s); m/z (ES^+) 271 (100%, $[\text{M}+\text{H}]^+$).

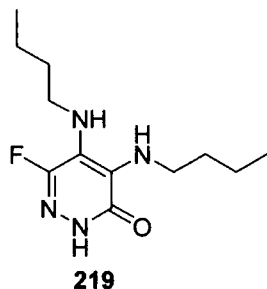
4-(Diethylamino)-6-fluoro-5-morpholinopyridazin-3(2H)-one **218**



4,6-Difluoro-5-morpholinopyridazin-3(2H)-one (50mg, 0.230mmol) was mixed with acetonitrile (3ml) and diethylamine (0.0595ml, 0.575mmol) in a 2-5 ml microwave vial, which was sealed and the mixture irradiated at 150°C for 60 minutes. After this period the solvent was evaporated, and the residue dissolved in dichloromethane (10ml). Water (10ml) was added and the organic layer separated on a hydrophobic frit. The aqueous layer was then extracted with further portions of dichloromethane ($2 \times 10\text{ml}$). The combined organic extracts were dried (MgSO_4), filtered and evaporated on a blowdown evaporator to yield a crude yellow solid. This was then purified by mass directed automated purification to yield 4-(diethylamino)-6-fluoro-5-morpholinopyridazin-3(2H)-one **218** (0.0311g, 50%) as a white solid; mp 140 – 142°C (Found $[\text{MH}]^+$ 271.15621. $\text{C}_{12}\text{H}_{19}\text{FN}_4\text{O}_2$ requires $[\text{MH}]^+$ 271.15648); δ_{H} (400MHz, CDCl_3) 1.09 (6H, t, $^3J_{\text{HH}}$ 7.3, NCH_2CH_3), 3.20 (4H, td, $^3J_{\text{HH}}$ 4.8, $^5J_{\text{HF}}$ 1.8, C2'(H)), 3.43 (4H, q, $^3J_{\text{HH}}$ 7.3, NCH_2CH_3), 3.78 (4H, t, $^3J_{\text{HH}}$ 4.8, C3'(H)), 10.17 (1H, br s, ring NH); δ_{C} (100MHz, CDCl_3) 13.9 (s, NCH_2CH_3), 45.6 (s, NCH_2CH_3), 49.8 (d, $^4J_{\text{CF}}$ 4.0, C2'), 67.2 (s, C3'), 132.0 (d, $^2J_{\text{CF}}$ 25.6, C5), 139.7 (d, $^3J_{\text{CF}}$ 10.4, C4), 153.5 (d, $^1J_{\text{CF}}$

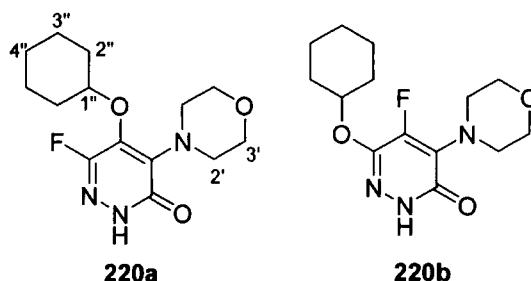
235.7, C6), 162.2 (s, C3); δ_F (376MHz, $CDCl_3$) -95.3 (1F, s); m/z (ES^+) 271 (100%, $[M+H]^+$).

4,5-Bis(butylamino)-6-fluoropyridazin-3(2H)-one 219



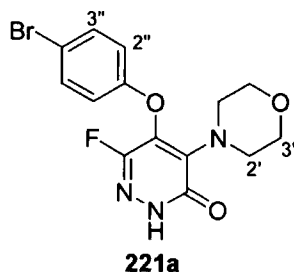
5-(butylamino)-4,6-difluoropyridazin-3(2H)-one (50mg, 0.246mmol) was dissolved in acetonitrile (1.5ml) in a 0.5 – 2ml microwave vial. After addition of butylamine (0.045g, 0.615mmol) the vial was sealed and irradiated at 150°C for 3 hours. After this period the solvent was evaporated and the crude material dissolved in dichloromethane (10ml). Water (10ml) was added, and the organic layer separated. The aqueous portion was washed with further portions of dichloromethane (3 × 10ml), and the combined organic extracts were dried ($MgSO_4$), filtered and evaporated to yield a crude yellow material. This was purified by mass directed automated purification to yield 4,5-bis(butylamino)-6-fluoropyridazin-3(2H)-one **219** (28.1mg, 45%) as a colourless oil; (Found $[MH]^+$ 257.17718, $C_{12}H_{22}N_4FO$ requires $[MH]^+$ 257.17722); δ_H (400MHz, $CDCl_3$) 0.93 (3H, t, $^3J_{HH}$ 7.1, $NCH_2CH_2CH_2CH_3$), 0.94 (3H, t, $^3J_{HH}$ 7.1, $NCH_2CH_2CH_2CH_3$), 1.38 (2H, sextet, $^3J_{HH}$ 7.1, $NCH_2CH_2CH_2CH_3$), 1.39 (2H, sextet, $^3J_{HH}$ 7.1, $NCH_2CH_2CH_2CH_3$), 1.52 (2H, pent, $^3J_{HH}$ 7.1, $NCH_2CH_2CH_2CH_3$), 3.41 (2H, pent, $^3J_{HH}$ 7.1, $NHCH_2CH_2CH_2CH_3$), 3.08 (2H, q, $^3J_{HH}$ 7.1, $NCH_2CH_2CH_2CH_3$), 3.26 (1H, br s, $NHBu$), 3.28 (2H, q, $^3J_{HH}$ 7.1, $NCH_2CH_2CH_2CH_3$), 5.54 (1H, br t, $^3J_{HH}$ 7.1, $NHBu$), 11.05 (1H, br s, ring NH); δ_C (100MHz, $CDCl_3$) 13.8 (s, $NCH_2CH_2CH_2CH_3$, 2nd peak underneath), 20.0 (s, $NCH_2CH_2CH_2CH_3$), 20.0 (s, $NCH_2CH_2CH_2CH_3$), 32.6 (s, $NCH_2CH_2CH_2CH_3$), 32.9 (s, $NCH_2CH_2CH_2CH_3$), 43.1 (s, $NHCH_2CH_2CH_2CH_3$), 44.1 (d, $^4J_{CF}$ 2.4, $NHCH_2CH_2CH_2CH_3$), 120.9 (d, $^2J_{CF}$ 31.2, C5), 139.4 (d, $^3J_{CF}$ 10.4, C4), 152.8 (d, $^1J_{CF}$ 226.9, C6), 159.9 (s, C3); δ_F (376MHz, $CDCl_3$) -102.6 (1F, s); m/z (ES^+) 257 (100%, $[M+H]^+$).

5-(Cyclohexyloxy)-6-fluoro-4-morpholinopyridazin-3(2H)-one **220a** and 6-(cyclohexyloxy)-5-fluoro-4-morpholinopyridazin-3(2H)-one **220b**



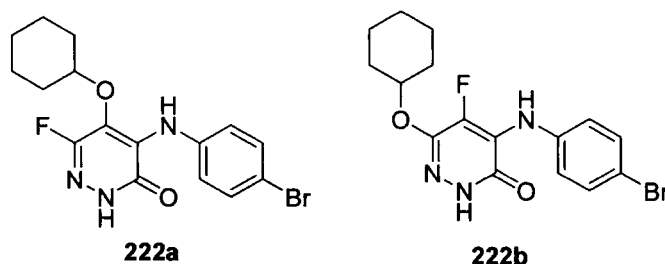
Cyclohexanol (0.23g, 2.30mmol) was mixed with sodium hydride (0.09g, 2.30mmol, 60% dispersion in mineral oil) and THF (10ml) in a Radleys Carousel tube under nitrogen with stirring. 5,6-difluoro-4-morpholinopyridazin-3(2H)-one (50mg, 0.230mmol) was added and the mixture heated to reflux for 64 hours. After this period the solvent was evaporated, and the residue dissolved in dichloromethane (10ml). Water (10ml) was added and the organic layer separated on a hydrophobic frit. The aqueous layer was then extracted with further portions of dichloromethane (2 × 10ml). The combined organic extracts were dried (MgSO₄), filtered and evaporated on a blowdown evaporator, followed by purification by mass directed automated purification to yield 5-(cyclohexyloxy)-6-fluoro-4-morpholinopyridazin-3(2H)-one **220a** (0.0127g, 19%) as a white solid; mp 175 – 177°C (Found [MH]⁺ 298.15604. C₁₄H₂₀FN₃O₃ requires [MH]⁺ 298.15615); δ_H (400MHz, MeOD) 1.28 – 1.98 (10H, m, cyclohexyl(H)), 3.53 (4H, t, ³J_{HH} 4.1, C2'(H)), 3.80 (4H, t, ³J_{HH} 4.1, C3'(H)), 4.10 (1H, m, C1''(H)); δ_C (100MHz, CDCl₃) 24.1 (s), 25.3 (s), 32.3 (s, C2''), 49.8 (s, C2'), 67.5 (s, C3'), 82.4 (d, ⁴J_{CF} 4.8, C1'), 134.2 (d, ²J_{CF} 28.8, C5), 139.6 (d, ³J_{CF} 8.8, C4), 152.8 (d, ¹J_{CF} 234.9, C6), 161.5 (s, C3); δ_F (376MHz, CDCl₃) -99.1 (1F, s); *m/z* (ES⁺) 298 (100%, [M+H]⁺).

A small sample of the minor isomer 6-(cyclohexyloxy)-5-fluoro-4-morpholinopyridazin-3(2H)-one **220b** was obtained (0.0082g, 12%) as a white solid; δ_H (400MHz, CDCl₃) 1.40 – 2.05 (10H, m, cyclohexyl(H)), 3.52 (4H, t, ³J_{HH} 4.6, C2'(H)), 3.78 (4H, t, ³J_{HH} 4.6, C3'(H)), 4.75 (1H, m, C1''(H)); δ_F (376MHz, CDCl₃) -141.8 (1F, s); *m/z* (ES⁺) 298 (100%, [M+H]⁺).

5-(4-Bromophenoxy)-6-fluoro-4-morpholinopyridazin-3(2H)-one 221a

4-Bromophenol (0.398g, 2.30mmol) was mixed with sodium hydride (0.090g, 2.30mmol, 60% dispersion in mineral oil) and THF (10ml) in a Radleys Carousel tube under nitrogen with stirring. 5,6-difluoro-4-morpholinopyridazin-3(2H)-one (50mg, 0.230mmol) was added and the mixture heated to reflux for 64 hours. After this period the solvent was evaporated, and the residue dissolved in dichloromethane (10ml). Water (10ml) was added and the organic layer separated on a hydrophobic frit. The aqueous layer was then extracted with further portions of dichloromethane ($2 \times 10\text{ml}$). The combined organic extracts were dried (MgSO_4), filtered and evaporated on a blowdown evaporator, followed by purification by mass directed automated purification to yield 5-(4-bromophenoxy)-6-fluoro-4-morpholinopyridazin-3(2H)-one **221a** (0.0196g, 23%) as a white solid; mp $173 - 174^\circ\text{C}$ (Found $[\text{}^{79}\text{Br}, \text{MH}]^+$ 370.01921. $\text{C}_{14}\text{H}_{13}\text{BrFN}_3\text{O}_3$ requires $[\text{}^{79}\text{Br}, \text{MH}]^+$ 370.01971); δ_{H} (400MHz, CDCl_3) 3.55 (4H, t, $^3J_{\text{HH}}$ 4.8, C2'(H)), 3.71 (4H, t, $^3J_{\text{HH}}$ 4.8, C3'(H)), 6.82 (2H, d, $^3J_{\text{HH}}$ 9.1, C2''(H)), 7.47 (2H, d, $^3J_{\text{HH}}$ 9.1, C3''(H)), 10.62 (1H, br s, ring NH); δ_{C} (100MHz, CDCl_3) 49.5 (s, C2'), 67.2 (s, C3'), 116.2 (s, ArC), 116.7 (s, ArC), 128.5 (d, $^2J_{\text{CF}}$ 30.4, C5), 130.1 (s, ArC), 140.0 (d, $^3J_{\text{CF}}$ 8.0, C4), 151.7 (d, $^1J_{\text{CF}}$ 235.7, C6), 155.7 (s, ArC), 160.6 (s, C3); δ_{F} (376MHz, CDCl_3) -101.1 (1F, s); m/z (ES^+) 372 (98%, $[\text{}^{81}\text{Br}, \text{M}+\text{H}]^+$), 370 (100, $[\text{}^{79}\text{Br}, \text{M}+\text{H}]^+$).

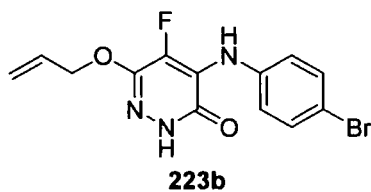
4-(4-Bromophenylamino)-5-(cyclohexyloxy)-6-fluoropyridazin-3(2H)-one **222a** and 4-(4-bromophenylamino)-6-(cyclohexyloxy)-5-fluoropyridazin-3(2H)-one **222b**



4-(4-bromophenylamino)-5,6-difluoropyridazin-3(2H)-one (100mg, 0.331mmol) was added to a 2-5ml microwave vial, along with tetrahydrofuran (3ml) and cyclohexanol (0.0874ml, 0.828mmol). Sodium hydride 0.0331g, 60% in mineral oil, 0.828mmol) was added under nitrogen. The vial was sealed after effervescence was completed, and the mixture irradiated at 120°C for 60 minutes. After this period the crude mixture was analysed by ^{19}F NMR and LC-MS, which showed conversion to products to be only 7%.

The reaction mixture contained 4-(4-bromophenylamino)-5-(cyclohexyloxy)-6-fluoropyridazin-3(2H)-one **222a**; δ_{F} (376MHz, CDCl_3) -99.6 (1F, s, F6); m/z (ES^+) 383 (98%, [^{81}Br , $\text{M}+\text{H}$] $^+$), 381 (100, [^{79}Br , $\text{M}+\text{H}$] $^+$), and 4-(4-bromophenylamino)-6-(cyclohexyloxy)-5-fluoropyridazin-3(2H)-one **222b**; δ_{F} (376MHz, CDCl_3) -136.0 (1F, s, F5); m/z (ES^+) 383 (98%, [^{81}Br , $\text{M}+\text{H}$] $^+$), 381 (100, [^{79}Br , $\text{M}+\text{H}$] $^+$).

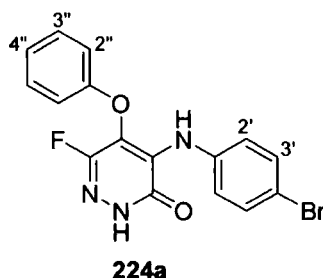
4-(4-Bromophenylamino)-6-(allyloxy)-5-fluoropyridazin-3(2H)-one **223b**



4-(4-Bromophenylamino)-5,6-difluoropyridazin-3(2H)-one **223b** (100mg, 0.331mmol) was added to a 2-5ml microwave vial, along with acetonitrile (3ml) and allyl alcohol (0.0563ml, 0.828mmol). Sodium hydride 0.0331g, 60% in mineral oil, 0.828mmol) was added under nitrogen. The vial was sealed after effervescence was completed, and the mixture irradiated at 120°C for 60 minutes. After this period the solvent was evaporated in a blowdown evaporator, and the crude residue dissolved in dichloromethane (10ml). Water (10ml) was added and the mixture separated on a hydrophobic frit. The aqueous layer was washed with further portions of dichloromethane ($2 \times 10\text{ml}$). The combined organic

extracts were then dried over MgSO_4 , filtered and evaporated to yield a crude yellow solid. This was then purified by mass directed automated purification, yielding 4-(4-bromophenylamino)-6-(allyloxy)-5-fluoropyridazin-3(2H)-one **223b** (0.0090g, 9%) as a white solid; (Found $[\text{}^{79}\text{Br}, \text{MH}]^+$ 340.00879. $\text{C}_{13}\text{H}_{11}\text{BrFN}_3\text{O}_2$ requires $[\text{}^{79}\text{Br}, \text{MH}]^+$ 340.00914); δ_{H} (400MHz, CDCl_3) 4.74 (2H, d, $^3J_{\text{HH}}$ 5.8, $\text{OCH}_2\text{CH}=\text{CH}_2$), 5.32 (1H, dd, $^3J_{\text{HH}}$ 10.5, $^2J_{\text{HH}}$ 1.2, $\text{OCH}_2\text{CH}=\text{CH}_2$), 5.43 (1H, dd, $^3J_{\text{HH}}$ 17.3, $^2J_{\text{HH}}$ 1.2, $\text{OCH}_2\text{CH}=\text{CH}_2$), 6.06 (1H, m, $\text{OCH}_2\text{CH}=\text{CH}_2$), 6.95 (2H, dd, $^3J_{\text{HH}}$ 8.5, $^6J_{\text{HF}}$ 3.5, $\text{C}2'(\text{H})$), 6.99 (1H, br s, NHAr), 7.44 (2H, d, $^3J_{\text{HH}}$ 8.5, $\text{C}3'(\text{H})$), 10.89 (1H, br s, ring NH); δ_{C} (100MHz, CDCl_3) 67.9 (s, $\text{OCH}_2\text{CH}=\text{CH}_2$), 117.2 (s), 118.8 (s), 122.9 (d, $^2J_{\text{CF}}$ 4.8, C4), 125.6 (s), 131.8 (s), 131.9 (s), 135.7 (d, $^1J_{\text{CF}}$ 271.6, C5), 137.6 (s), 148.5 (d, $^2J_{\text{CF}}$ 13.5, C6), 159.6 (d, $^3J_{\text{CF}}$ 10.4, C3); δ_{F} (376MHz, CDCl_3) -137.1 (1F, s, F5); m/z (ES^+) 342 (98%, $[\text{}^{81}\text{Br}, \text{M}+\text{H}]^+$) 340 (100, $[\text{}^{79}\text{Br}, \text{M}+\text{H}]^+$).

4-(4-Bromophenylamino)-6-fluoro-5-phenoxy pyridazin-3(2H)-one **224a**

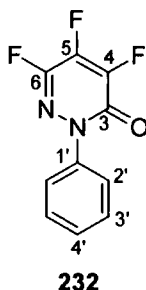


4-(4-Bromophenylamino)-5,6-difluoropyridazin-3(2H)-one (100mg, 0.331mmol) was added to a 2-5ml microwave vial, along with acetonitrile (3ml) and sodium phenoxide (0.0961g, 0.828mmol). The vial was sealed after effervescence was completed, and the mixture irradiated at 120°C for 60 minutes. After this period the solvent was evaporated in a blowdown evaporator, and the crude residue dissolved in dichloromethane (10ml). Water (10ml) was added and the mixture separated on a hydrophobic frit. The aqueous layer was washed with further portions of dichloromethane ($2 \times 10\text{ml}$). The combined organic extracts were then dried over MgSO_4 , filtered and evaporated to yield a crude yellow solid. This was then purified by mass directed automated purification, yielding 4-(4-bromophenylamino)-6-fluoro-5-phenoxy pyridazin-3(2H)-one **224a** (0.0087g, 7%) as a white solid; mp $164 - 166^\circ\text{C}$ (Found $[\text{}^{79}\text{Br}, \text{MH}]^+$ 376.00906. $\text{C}_{16}\text{H}_{11}\text{BrFN}_3\text{O}_2$ requires $[\text{}^{79}\text{Br}, \text{MH}]^+$ 376.00914); δ_{H} (400MHz, CDCl_3) 6.50 (2H, d, $^3J_{\text{HH}}$ 7.5, $\text{C}2''(\text{H})$), 6.81 (2H, d, $^3J_{\text{HH}}$ 8.5, $\text{C}2'(\text{H})$), 6.96 (1H, t, $^3J_{\text{HH}}$ 7.5, $\text{C}4''(\text{H})$), 7.14 (2H, t, $^3J_{\text{HH}}$ 7.5, $\text{C}3''(\text{H})$) 7.25 (1H, br s,

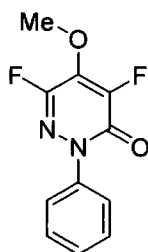
NHAr), 7.27 (2H, d, $^3J_{\text{HH}}$ 8.5, C3'(H), 9.81 (1H, br s, ring NH); δ_{F} (376MHz, CDCl_3) -100.1 (1F, s, F6); m/z (ES^-) 376 (100%, [^{81}Br , M+H] $^+$) 374 (92, [^{79}Br , M+H] $^+$).

7.3 Experimental to Chapter 3

4,5,6-Trifluoro-2-phenylpyridazin-3(2H)-one **232**

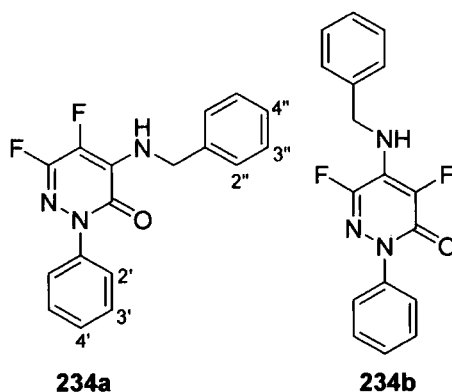


4,5,6-Trifluoropyridazin-3(2H)-one (0.25g, 1.67mmol) was mixed with lead (IV) acetate (0.81g, 1.83mmol) and zinc (II) chloride (0.23g, 1.67mmol), which were dissolved in anhydrous benzene (20ml) under argon with stirring. The mixture was heated to reflux for 8 hours before being allowed to cool. Water (20ml) was added, followed by dichloromethane (20ml), and the layers separated. The aqueous layer was then extracted with dichloromethane (3 × 20ml) and the combined organic extracts dried (MgSO_4), filtered and evaporated to yield a crude yellow material. This was purified by flash column chromatography using hexane and ethyl acetate (4:1) as elutant to yield 4,5,6-trifluoro-2-phenylpyridazin-3(2H)-one **232** (0.16g, 42%) as a white solid; mp 120 – 122°C (Found C, 52.9; H, 2.2; N, 12.2. $\text{C}_{10}\text{H}_5\text{F}_3\text{N}_2\text{O}$ requires C, 53.1; H, 2.2; N, 12.4%); δ_{H} (500MHz, CDCl_3) 7.43 (1H, t, $^3J_{\text{HH}}$ 7.7, C4'(H)), 7.50 (2H, t, $^3J_{\text{HH}}$ 7.7, C2'(H)), 7.57 (2H, d, $^3J_{\text{HH}}$ 7.7, C3'(H)); δ_{C} (125MHz, CDCl_3) 124.9 (s, ArC), 129.2 (s, ArC), 129.2 (s, ArC), 139.0 (ddd, $^1J_{\text{CF}}$ 288.5, $^2J_{\text{CF}}$ 33.9, $^2J_{\text{CF}}$ 10.3, C5), 139.4 (s, C1'), 144.9 (ddd, $^1J_{\text{CF}}$ 258.4, $^2J_{\text{CF}}$ 19.9, $^3J_{\text{CF}}$ 3.9, C4), 145.0 (ddd, $^1J_{\text{CF}}$ 251.0, $^2J_{\text{CF}}$ 26.6, $^3J_{\text{CF}}$ 4.7, C6), 155.2 (dd, $^2J_{\text{CF}}$ 21.3, $^3J_{\text{CF}}$ 4.7, C3); δ_{F} (188MHz, CDCl_3) -101.2 (1F, dd, $^3J_{\text{FF}}$ 27.1, $^4J_{\text{FF}}$ 15.4, F6), -133.5 (1F, dd, $^3J_{\text{FF}}$ 17.2, $^4J_{\text{FF}}$ 15.4, F4), -145.6 (1F, dd, $^3J_{\text{FF}}$ 27.1, $^3J_{\text{FF}}$ 17.2, F5); m/z (EI^+) 226 (30%, [M] $^+$), 225 (33, [$\text{M}-\text{H}$] $^+$), 77 (100, [Ph] $^+$).

4,6-Difluoro-5-methoxy-2-phenylpyridazin-3(2H)-one 233b**233b**

4,5,6-Trifluoro-2-phenylpyridazin-3(2H)-one (0.25g, 1.11mmol) was mixed with sodium methoxide (0.12g, 2.21mmol) and dissolved in anhydrous methanol (20ml) before stirring at room temperature for 8 hours. The solvent was then evaporated and the crude material dissolved in dichloromethane (20ml) and water (20ml), before separation of the layers. The aqueous layer was then extracted with further portions of dichloromethane (3 × 20ml), and the organic extracts were combined, dried (MgSO₄), filtered and evaporated to yield a crude yellow material (0.23g), which was purified by recrystallisation from hexane to yield **4,6-difluoro-5-methoxy-2-phenylpyridazin-3(2H)-one 233b** (0.17g, 64%) as a white solid; mp 88 – 90°C (Found C, 55.2; H, 3.4; N, 12.0. C₁₁H₈F₂N₂O₂ requires C, 55.5; H, 3.4; N, 11.8%); ν_{\max} / cm⁻¹ 1036, 1100, 1417, 1654 (CO amide); δ_{H} (500MHz, CDCl₃) 4.27 (3H, d, ⁵J_{HF} 4.8, OCH₃), 7.38 (1H, t, ³J_{HH} 8.1, C4'(H4)), 7.54 (2H, t, ³J_{HH} 8.1, C2'(H)), 7.59 (2H, d, ³J_{HH} 8.1, C3'(H)); δ_{C} (125MHz, CDCl₃) 61.1 (d, ⁴J_{CF} 8.1, OCH₃), 124.9 (s, ArC), 128.6 (s, ArC), 129.0 (s, ArC), 136.5 (dd, ²J_{CF} 31.0, ²J_{CF} 6.8, C5), 139.7 (s, C1'), 144.7 (dd, ¹J_{CF} 256.9, ³J_{CF} 10.5, C4), 147.4 (dd, ¹J_{CF} 240.6, ³J_{CF} 8.5, C6), 155.2 (d, ²J_{CF} 23.8, C3); δ_{F} (188MHz, CDCl₃) -98.3 (1F, dd, ⁴J_{FF} 20.2, F6), -141.0 (1F, dq, ⁴J_{FF} 20.2, ⁵J_{HF} 4.8, F4); m/z (ES⁺) 239 (100%, [M+H]⁺).

4-(Benzylamino)-5,6-difluoro-2-phenylpyridazin-3(2H)-one **234a** and 5-(benzylamino)-4,6-difluoro-2-phenylpyridazin-3(2H)-one **234b**

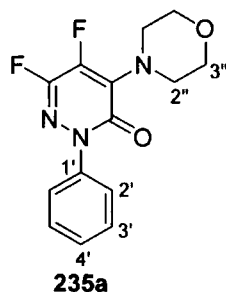


4,5,6-Trifluoro-2-phenylpyridazin-3(2H)-one (0.25g, 1.11mmol) dissolved in anhydrous acetonitrile (20ml) before the addition of benzylamine (0.24ml, 2.21mmol) and stirring at room temperature for 8 hours. The solvent was then evaporated and the crude material dissolved in dichloromethane (20ml) and water (20ml), before separation of the layers. The aqueous layer was then extracted with further portions of dichloromethane (3 × 20ml), and the organic extracts were combined, dried (MgSO₄), filtered and evaporated to yield a crude brown material (0.29g), which was purified by flash column chromatography using hexane and ethyl acetate (4:1) as elutant to yield 4-(benzylamino)-5,6-difluoro-2-phenylpyridazin-3(2H)-one **234a** (0.14g, 40%) as a white solid; mp 116 – 117°C (Found C, 65.3; H, 4.2; N, 13.4. C₁₇H₁₃F₂N₃O requires C, 65.2; H, 4.2; N, 13.4%); ν_{\max} / cm⁻¹ 1131, 1345, 1449, 1662 (CO amide); δ_{H} (500MHz, CDCl₃) 4.74 (2H, d, ³J_{HH} 6.3, NHCH₂Ph), 6.05 (1H, br s, NHBn), 7.33 (3H, m, ArH), 7.38 (3H, m, ArH), 7.46 (2H, t, ³J_{HH} 7.8, C3'(H)), 7.57 (2H, d, ³J_{HH} 7.8, C2'(H)); δ_{C} (125MHz, CDCl₃) 48.2 (d, ⁴J_{CF} 6.5, NHCH₂Ph), 125.4 (s, ArC), 127.5 (s, ArC), 128.2 (s, ArC), 128.6 (s, ArC), 129.0 (s, ArC), 129.1 (s, ArC), 130.5 (dd, ¹J_{CF} 260.7, ²J_{CF} 33.3, C5), 132.3 (d, ²J_{CF} 8.8, C4), 137.9 (s, ArC), 140.7 (s, ArC), 147.8 (dd, ¹J_{CF} 230.8, ²J_{CF} 17.4, C6), 157.8 (d, ³J_{CF} 10.9, C3); δ_{F} (658MHz, CDCl₃) -104.7 (1F, d, ³J_{FF} 28.9, F6), -162.5 (1F, d, ³J_{FF} 28.9, F5); m/z (ES⁺) 314 (100%, [M+H]⁺).

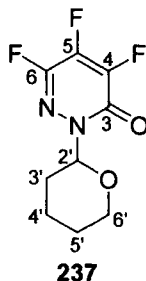
The minor isomer 5-(benzylamino)-4,6-difluoro-2-phenylpyridazin-3(2H)-one **234b** was also isolated (0.09g, 30%) as a white solid; mp 171 – 173°C (Found C, 65.1; H, 4.3; N, 13.6. C₁₇H₁₃F₂N₃O requires C, 65.2; H, 4.2; N, 13.4%); ν_{\max} / cm⁻¹ 1115, 1357, 1510, 1626; δ_{H} (700MHz, CDCl₃) 4.51 (1H, br s, NHBn), 4.69 (2H, dd, ³J_{HH} 6.0, ⁵J_{HF} 1.9, NHCH₂Ph), 7.35 (4H, m, ArH), 7.41 (2H, m, ArH), 7.44 (2H, t, ³J_{HH} 8.2, C3'(H)), 7.60 (2H, d, ³J_{HH} 8.2,

C2'(H)); δ_C (175MHz, $CDCl_3$) 48.8 (d, $^4J_{CF}$ 7.2, $NHCH_2Ph$), 124.9 (s, ArC), 126.1 (dd, $^2J_{CF}$ 31.1, $^2J_{CF}$ 8.4, C5), 127.9 (s, ArC), 128.2 (s, ArC), 128.6 (s, ArC), 129.0 (s, ArC), 129.3 (s, ArC), 137.5 (s, ArC), 139.8 (dd, $^1J_{CF}$ 245.2, $^3J_{CF}$ 4.1, C4), 140.1 (s, ArC), 146.0 (dd, $^1J_{CF}$ 243.0, $^3J_{CF}$ 11.0, C6), 155.3 (d, $^2J_{CF}$ 22.8, C3); δ_F (658MHz, $CDCl_3$) -99.5 (1F, d, $^3J_{FF}$ 22.1, F6), -146.8 (1F, d, $^3J_{FF}$ 22.1, $^5J_{HF}$ 1.9, F4); m/z (ES⁺) 314 (100%, $[M+H]^+$).

5,6-Difluoro-4-morpholino-2-phenylpyridazin-3(2H)-one 235a

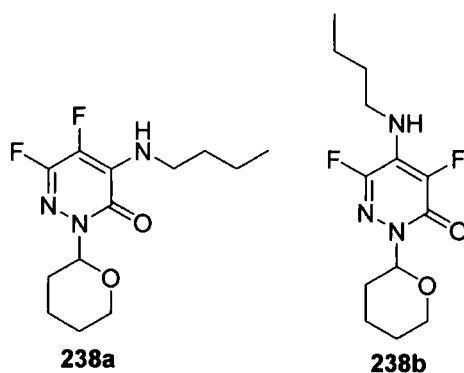


4,5,6-Trifluoro-2-phenylpyridazin-3(2H)-one (0.25g, 1.11mmol) was dissolved in anhydrous acetonitrile (20ml) before the addition of morpholine (0.19g, 2.21mmol) and stirring at room temperature for 8 hours. The solvent was then evaporated and the crude material dissolved in dichloromethane (20ml) and water (20ml), before separation of the layers. The aqueous layer was then extracted with further portions of dichloromethane (3 × 20ml), and the organic extracts were combined, dried ($MgSO_4$), filtered and evaporated to yield a crude yellow material (0.27g), which was purified by recrystallisation from hexane to yield **5,6-difluoro-4-morpholino-2-phenylpyridazin-3(2H)-one 235a** (0.19g, 58%) as a white solid; mp 116 – 118°C (Found C, 57.1; H, 4.5; N, 14.3. $C_{14}H_{13}F_2N_3O_2$ requires C, 57.3; H, 4.5; N, 14.3%); ν_{max} / cm^{-1} 1111, 1260, 1492, 1591, 1626 (CO amide); δ_H (700MHz, $CDCl_3$) 3.65 (4H, m, C2''(H)), 3.82 (4H, t, $^3J_{HH}$ 4.7, C3''(H)), 7.38 (1H, t, $^3J_{HH}$ 7.6, C4'(H)), 7.46 (2H, t, $^3J_{HH}$ 7.6, C2'(H)), 7.49 (2H, d, $^3J_{HH}$ 7.6, C3'(H)); δ_C (175MHz, $CDCl_3$) 49.8 (d, $^4J_{CF}$ 4.4, C2'), 61.1 (d, $^5J_{CF}$ 1.5, C3''), 125.8 (s, ArC), 128.6 (s, ArC), 129.1 (s, ArC), 134.8 (d, $^2J_{CF}$ 7.5, C4), 137.4 (dd, $^1J_{CF}$ 268.7, $^2J_{CF}$ 31.7, C5), 140.8 (s, C1'), 147.3 (dd, $^1J_{CF}$ 233.6, $^2J_{CF}$ 19.1, C6), 159.0 (d, $^3J_{CF}$ 9.5, C3); δ_F (658MHz, $CDCl_3$) -105.8 (1F, d, $^4J_{FF}$ 28.0, F6), -147.5 (1F, dt, $^4J_{FF}$ 28.0, $^5J_{HF}$ 2.3, F4); m/z (EI) 293 (12%, $[M]^+$), 275 (60), 222 (46), 208 (53), 86 (40), 77 (100, $[Ph]^+$).

4,5,6-Trifluoro-2-(tetrahydro-2H-pyran-2-yl)pyridazin-3(2H)-one 237

4,5,6-Trifluoropyridazin-3(2H)-one (0.50g, 3.33mmol) and *p*-toluenesulfonic acid (0.051g, 0.26mmol) were dissolved in tetrahydrofuran (10ml) and 3,4-dihydro-2H-pyran (0.76ml, 8.33mmol) was added. The mixture was heated to reflux for 5 hours, after which it was allowed to cool and the solvent evaporated. The crude material was dissolved in ethyl acetate (20ml) and washed with aqueous sodium hydroxide solution (2M, 20ml). The aqueous layer was then extracted with ethyl acetate (3 × 20ml) before the combined organic extracts were dried (MgSO₄), filtered and evaporated to yield a crude yellow oil. This was purified by flash column chromatography using hexane and ethyl acetate (9:1, 500ml, 4:1, 500ml) as elutant to yield 4,5,6-trifluoro-2-(tetrahydro-2H-pyran-2-yl)pyridazin-3(2H)-one **237** (0.47g, 60%) as a white solid; mp 56 – 58°C (Found C, 46.4; H, 4.0; N, 11.9. C₉H₉F₃N₂O₂ requires C, 46.2; H, 3.9; N, 12.0%); ν_{\max} / cm⁻¹ 1084, 1306, 1458, 1589, 1698 (CO amide); δ_{H} (500MHz, CDCl₃) 1.55 (1H, m), 1.66 (3H, m), 2.05 (2H, m), 3.69 (1H, dm, ²J_{HH} 12.0, ³J_{HH} 2.6, C6'(H)), 4.07 (1H, dm, ²J_{HH} 12.0, C6'(H)), 5.92 (1H, dd, ³J_{HH} 11.3, ³J_{HH} 1.8, C2'(H)); δ_{C} (125MHz, CDCl₃) 22.5 (s, C4'), 24.7 (s, CH₂), 28.3 (s, CH₂), 68.9 (s, C6'), 83.0 (t, ⁴J_{CF} 1.5, C2'), 139.1 (ddd, ¹J_{CF} 289.0, ²J_{CF} 36.3, ³J_{CF} 11.2, C5), 144.3 (ddd, ¹J_{CF} 269.5, ²J_{CF} 9.6, ³J_{CF} 3.5, C4), 147.4 (ddd, ¹J_{CF} 238.6, ²J_{CF} 17.0, ³J_{CF} 3.9, C6), 158.0 (dd, ²J_{CF} 20.9, ³J_{CF} 4.9, C3); δ_{F} (376MHz, CDCl₃) -100.8 (1F, dd, ³J_{FF} 26.4, ⁴J_{FF} 15.2, F6), -134.7 (1F, dd, ³J_{FF} 15.2, ⁴J_{FF} 15.2, F4), -145.6 (1F, dd, ³J_{FF} 26.4, ⁴J_{FF} 15.2, F5); *m/z* (EI) 234 (1%, [M]⁺), 150 (18%, [M-THP]⁺), 85 (100).

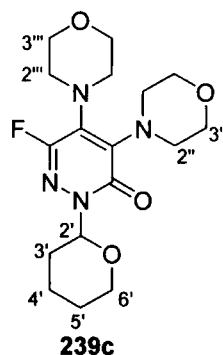
4-(Butylamino)-5,6-difluoro-2-(tetrahydro-2H-pyran-2-yl)pyridazin-3(2H)-one **238a** and 5-(butylamino)-4,6-difluoro-2-(tetrahydro-2H-pyran-2-yl)pyridazin-3(2H)-one **238b**



A Greenhouse Plus tube was charged with 4,5,6-trifluoro-2-(tetrahydro-2H-pyran-2-yl)pyridazin-3(2H)-one (100mg, 0.427mmol) and dissolved in acetonitrile (5ml). Butylamine (0.0844ml, 0.854mmol) was added under an atmosphere of nitrogen, and the mixture stirred at room temperature for 20 hours. After this period the solvent was evaporated in a blowdown evaporator, before being redissolved in dichloromethane (5ml). Water (5ml) was added and the organic layer separated on a hydrophobic frit. The aqueous layer was washed with further portions of dichloromethane (3 × 5ml), and the organic extracts dried over MgSO₄. After filtration and evaporation, the crude material was purified by flash column chromatography (Cyclohexane : ethyl acetate gradient 10% to 33% ethyl acetate over 20 minutes). This yielded the major isomer 4-(butylamino)-5,6-difluoro-2-(tetrahydro-2H-pyran-2-yl)pyridazin-3(2H)-one **238a** (0.0560g, 46%) as a white solid; mp 133 – 135°C (Found [MH]⁺ 288.1524. C₁₃H₁₉F₂N₃O₂ requires [MH]⁺ 288.1510); δ_H (400MHz, CDCl₃) 0.95 (3H, t, ³J_{HH} 7.4, NHCH₂CH₂CH₂CH₃), 1.40 (2H, sextet, ³J_{HH} 7.4, NHCH₂CH₂CH₂CH₃), 1.50 – 1.75 (6H, m), 2.03 (1H, m), 2.17 (1H, m), 3.50 (2H, q, ³J_{HH} 6.5, NHCH₂CH₂CH₂CH₃), 3.70 (1H, dt, ²J_{HH} 11.6, ³J_{HH} 1.5, C6'(H)), 4.11 (1H, dd, ²J_{HH} 11.6, ³J_{HH} 4.0, C6'(H)), 5.52 (1H, br t, ³J_{HH} 6.5, NHCH₂CH₂CH₂CH₃), 5.93 (1H, d, ³J_{HH} 10.5, C2'(H)); δ_C (100MHz, CDCl₃) 13.6 (s, NHCH₂CH₂CH₂CH₃), 19.7 (s, CH₂), 22.7 (s, CH₂), 24.8 (s, CH₂), 28.3 (s, CH₂), 32.5 (d, ⁵J_{CF} 2.4, NHCH₂CH₂CH₂CH₃), 43.8 (d, ⁴J_{CF} 6.4, NHCH₂CH₂CH₂CH₃), 68.6 (s, C6'), 83.4 (s, C2'), 129.8 (dd, ¹J_{CF} 258.8, ²J_{CF} 33.6, C5), 131.8 (d, ²J_{CF} 8.8, C4), 147.4 (dd, ¹J_{CF} 230.1, ²J_{CF} 16.8, C6), 158.0 (d, ³J_{CF} 11.2, C3); δ_F (376MHz, CDCl₃) -105.2 (1F, d, ³J_{FF} 28.7, F6), -165.2 (1F, d, ³J_{FF} 28.7, F5); *m/z* (ES⁺) 288 ([M+H]⁺, 70%), 245 (73), 204 ([M-THP+H]⁺, 100).

The minor product was identified as 5-(butylamino)-4,6-difluoro-2-(tetrahydro-2H-pyran-2-yl)pyridazin-3(2H)-one **238b** (0.0423g, 34%) as a white solid; mp 115 – 116°C (Found $[MH]^+$ 288.1515. $C_{13}H_{19}F_2N_3O_2$ requires $[MH]^+$ 288.1524); δ_H (400MHz, $CDCl_3$) 0.94 (3H, t, $^3J_{HH}$ 7.5, $NHCH_2CH_2CH_2CH_3$), 1.38 (2H, sextet, $^3J_{HH}$ 7.5, $NHCH_2CH_2CH_2CH_3$), 1.51 – 1.73 (6H, m), 2.05 (2H, m), 3.45 (2H, qd, $^3J_{HH}$ 9.0, $^4J_{HF}$ 2.0, $NHCH_2CH_2CH_2CH_3$), 3.70 (1H, td, $^2J_{HH}$ 11.5, $^3J_{HH}$ 2.5, C6'(H)), 4.06 (1H, m, C6'(H)), 4.30 (1H, br t, $^3J_{HH}$ 9.0, $NHCH_2CH_2CH_2CH_3$), 5.92 (1H, ddd, $^3J_{HH}$ 10.5, $^3J_{HH}$ 2.0, $^4J_{HH}$, C2'(H)); δ_C (100MHz, $CDCl_3$) 13.6 (s, $NHCH_2CH_2CH_2CH_3$), 19.6 (s, CH_2), 22.7 (s, CH_2), 24.8 (s, CH_2), 28.3 (s, CH_2), 32.5 (d, $^5J_{CF}$ 2.4, $NHCH_2CH_2CH_2CH_3$), 44.2 (d, $^4J_{CF}$ 6.4, $NHCH_2CH_2CH_2CH_3$), 68.6 (s, C6'), 81.7 (s, C2'), 126.5 (dd, $^2J_{CF}$ 30.4, $^2J_{CF}$ 8.0, C5), 138.5 (dd, $^1J_{CF}$ 243.7, $^3J_{CF}$ 10.4, C4), 145.6 (dd, $^1J_{CF}$ 232.5, $^3J_{CF}$ 10.4, C6), 155.3 (d, $^2J_{CF}$ 22.4, C3); δ_F (376MHz, $CDCl_3$) -100.0 (1F, d, $^3J_{FF}$ 22.4, F6), -150.5 (1F, d, $^3J_{FF}$ 22.4, F5); m/z (ES^+) 288 (11%, $[M+H]^+$) 245 (45, $[M-THP+MeCN]^+$), 204 (100, $[M-THP+H]^+$).

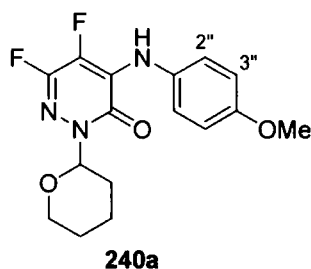
6-Fluoro-2-(tetrahydro-2H-pyran-2-yl)-4,5-dimorpholinopyridazin-3(2H)-one **239c**



A Greenhouse Plus tube was charged with 4,5,6-trifluoro-2-(tetrahydro-2H-pyran-2-yl)pyridazin-3(2H)-one (100mg, 0.427mmol) and dissolved in acetonitrile (5ml). Morpholine (0.075ml, 0.854mmol) was added under an atmosphere of nitrogen, and the mixture stirred at room temperature for 20 hours. After this period the solvent was evaporated in a blowdown evaporator, before being redissolved in dichloromethane (5ml). Water (5ml) was added and the organic layer separated on a hydrophobic frit. The aqueous layer was washed with further portions of dichloromethane (3 × 5ml), and the organic extracts dried over $MgSO_4$. After filtration and evaporation, the crude material was dissolved in 1ml DMSO / Methanol (1:1) and purified by mass directed automated purification. This yielded the major isomer 6-fluoro-2-(tetrahydro-2H-pyran-2-yl)-4,5-

dimorpholinopyridazin-3(2H)-one **239c** (0.0703g, 45%) as a white solid; mp 133 – 134°C (Found $[\text{MH}]^+$ 369.19311. $\text{C}_{17}\text{H}_{25}\text{FN}_4\text{O}_4$ requires $[\text{MH}]^+$ 369.19326); δ_{H} (400MHz, CDCl_3) 1.52 (1H, m), 1.65 (3H, ~ t (peak underneath), $^2J_{\text{HH}}$ 11.8), 2.00 (1H, m), 2.13 (1H, m), 3.11 (4H, m, $\text{C}2''/\text{C}2'''(\text{H})$), 3.40 (4H, t, $^3J_{\text{HH}}$ 4.5, $\text{C}2''/\text{C}2'''(\text{H})$), 3.68 (1H, dt, $^2J_{\text{HH}}$ 11.4, $^3J_{\text{HH}}$ 2.3, $\text{C}6'(\text{H})$), 3.75 (4H, t, $^3J_{\text{HH}}$ 4.8, $\text{C}3''/\text{C}3'''(\text{H})$), 3.77 (4H, t, $^3J_{\text{HH}}$ 4.5, $\text{C}3''/\text{C}3'''(\text{H})$), 4.08 (1H, ddd, $^2J_{\text{HH}}$ 11.4, $^3J_{\text{HH}}$ 2.0, 2.0, $\text{C}6'(\text{H})$), 5.82 (1H, ddd, $^3J_{\text{HH}}$ 10.8, $^3J_{\text{HH}}$ 2.0, $^4J_{\text{HH}}$ 2.0, $\text{C}2'(\text{H})$); δ_{C} (100MHz, CDCl_3) 22.8 (s, CH_2), 24.8 (s, CH_2), 28.3 (s, CH_2), 49.9 (s, $\text{C}2''$), 50.0 (d, $^4J_{\text{CF}}$ 4.0, $\text{C}2'''$), 67.0 (s, $\text{C}3''/\text{C}3'''/\text{C}6'$), 67.4 (s, $\text{C}3''/\text{C}3'''/\text{C}6'$), 68.7 (s, $\text{C}3''/\text{C}3'''/\text{C}6'$), 82.7 (s, $\text{C}2'$), 129.8 (d, $^2J_{\text{CF}}$ 28.0, C5), 140.9 (d, $^3J_{\text{CF}}$ 11.2, C4), 152.3 (d, $^1J_{\text{CF}}$ 238.1, C6), 159.3 (s, C3); δ_{F} (376MHz, CDCl_3) -91.4 (1F, s, F6); m/z (ES^+) 369 (33%, $[\text{M}+\text{H}]^+$), 285 (100, $[\text{M}+\text{H}-\text{THP}]^+$).

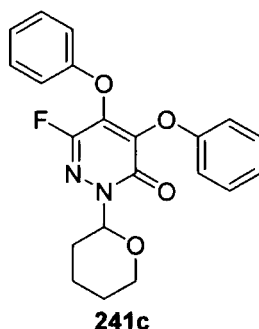
4-(4-Methoxyphenylamino)-5,6-difluoro-2-(tetrahydro-2H-pyran-2-yl)pyridazin-3(2H)-one **240a**



A Greenhouse Plus tube was charged with 4,5,6-trifluoro-2-(tetrahydro-2H-pyran-2-yl)pyridazin-3(2H)-one (100mg, 0.427mmol) and *p*-anisidine (0.1052g, 0.854mmol). The mixture was dissolved in acetonitrile (5ml) under an atmosphere of nitrogen, and stirred at room temperature for 20 hours. After this period the solvent was evaporated in a blowdown evaporator, before being redissolved in dichloromethane (5ml). Water (5ml) was added and the organic layer separated on a hydrophobic frit. The aqueous layer was washed with further portions of dichloromethane (3 × 5ml), and the organic extracts dried over MgSO_4 . After filtration and evaporation, the crude material was purified by mass directed automated purification by flash column chromatography (Elutant ethyl acetate : hexane – 10% to 33% EtOAc over 20 minutes). This yielded the major isomer *4-(4-methoxyphenylamino)-5,6-difluoro-2-(tetrahydro-2H-pyran-2-yl)pyridazin-3(2H)-one* **240a** (0.029g, 20%) as a white solid; mp 162 – 164°C; (Found $[\text{MH}]^+$ 338.13123; $\text{C}_{16}\text{H}_{17}\text{F}_2\text{N}_3\text{O}_3$ requires $[\text{MH}]^+$ 338.13107). δ_{H} (400MHz, CDCl_3) 1.56 (1H, m), 1.67 (3H, m), 1.76 (1H,

m), 2.03 (1H, m), 2.10 (1H, d, $^2J_{\text{HH}}$ 10.8), 3.72 (1H, ddd, $^2J_{\text{HH}}$ 11.4, $^3J_{\text{HH}}$ 11.5, $^3J_{\text{HH}}$ 2.5, C6'(H)), 3.80 (3H, s, CH₃), 4.09 (1H, ddd, $^2J_{\text{HH}}$ 11.4, $^3J_{\text{HH}}$ 2.0, $^3J_{\text{HH}}$ 1.8, C6'(H)), 5.96 (1H, ddd, $^3J_{\text{HH}}$ 10.8, $^3J_{\text{HH}}$ 1.8, $^4J_{\text{HH}}$ 1.8, C2'(H)), 6.86 (2H, d, $^3J_{\text{HH}}$ 8.9, C2''(H)), 7.03 (2H, dd, $^3J_{\text{HH}}$ 8.9, $^4J_{\text{HH}}$ 2.3, ArH); δ_{C} (100MHz, CDCl₃) 22.7 (s, CH₂), 24.8 (s, CH₂), 28.4 (s, CH₂), 55.5 (s, CH₂), 68.7 (s, CH₂), 83.0 (s, CH), 114.1 (s, ArCH), 123.8 (dd, $^2J_{\text{CF}}$ 30.4, $^3J_{\text{CF}}$ 8.0, C4), 124.5 (d, $^4J_{\text{CF}}$ 3.2), 130.3 (s, ArCH), 131.6 (s, ArC), 140.1 (dd, $^1J_{\text{CF}}$ 252.5, $^2J_{\text{CF}}$ 10.4, C5), 146.0 (dd, $^1J_{\text{CF}}$ 234.0, C6), 155.1 (d, $^3J_{\text{CF}}$ 21.6), 157.7 (s, ArC); δ_{F} (376MHz, CDCl₃) -97.4 (1F, d, $^3J_{\text{FF}}$ 20.1, F6), -136.1 (1F, d, $^3J_{\text{FF}}$ 20.1, F5); m/z (ES⁺) 338 (45%, [M+H]⁺), 295 (60, [M+MeCN-THP]⁺), 254 (100, [M+H-THP]⁺).

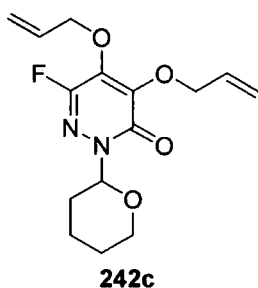
6-Fluoro-2-(tetrahydro-2H-pyran-2-yl)-4,5-diphenoxypyridazin-3(2H)-one 241c



A Greenhouse Plus tube was charged with 4,5,6-trifluoro-2-(tetrahydro-2H-pyran-2-yl)pyridazin-3(2H)-one (100mg, 0.427mmol) and sodium phenoxide (0.0991g, 0.854mmol). The mixture was dissolved in acetonitrile (5ml) under an atmosphere of nitrogen, and stirred at room temperature for 20 hours. After this period the solvent was evaporated in a blowdown evaporator, before being redissolved in dichloromethane (5ml). Water (5ml) was added and the organic layer separated on a hydrophobic frit. The aqueous layer was washed with further portions of dichloromethane (3 × 5ml), and the organic extracts dried over MgSO₄. After filtration and evaporation, the crude material was dissolved in 1ml DMSO / Methanol (1:1) and purified by mass directed automated purification. After elution through a NH₂ SPE column to remove residual TFA and solvent evaporation, this yielded the major isomer *6-fluoro-2-(tetrahydro-2H-pyran-2-yl)-4,5-diphenoxypyridazin-3(2H)-one 241c* (0.0891g, 55%) as a colourless oil; (Found [MH]⁺ 383.1404. C₁₇H₂₅FN₄O₄ requires [MH]⁺ 383.1407); δ_{H} (400MHz, CDCl₃) 1.57 (1H, dd, $^2J_{\text{HH}}$ 7.0, $^3J_{\text{HH}}$ 2.0), 1.71 (3H, m), 2.05 (1H, m), 2.19 (1H, m), 3.72 (1H, td, $^2J_{\text{HH}}$ 11.5, $^3J_{\text{HH}}$ 2.5, C6'(H)), 4.14 (1H, ddd, $^2J_{\text{HH}}$ 11.5, $^3J_{\text{HH}}$ 2.5, $^3J_{\text{HH}}$ 1.8, C6'(H)), 5.99 (1H, ddd, $^3J_{\text{HH}}$ 10.8,

$^3J_{\text{HH}}$ 2.0, $^4J_{\text{HH}}$ 2.0, C2'(H)), 6.83 (2H, dm, $^3J_{\text{HH}}$ 6.8, ArH), 6.88 (2H, dd, $^3J_{\text{HH}}$ 8.8, $^4J_{\text{HH}}$ 1.3, ArH), 7.02 (2H, dd, $^3J_{\text{HH}}$ 7.3, 7.3, ArH), 7.23 (4H, m, ArH); δ_{C} (100MHz, CDCl_3) 22.7 (s, CH_2), 24.8 (s, CH_2), 28.4 (s, CH_2), 68.8 (s, CH_2), 82.9 (s, C2'), 116.4 (s, ArC), 116.6 (s, ArC), 123.9 (s, ArC), 124.4 (s, ArC), 129.3 (s, ArH), 129.6 (s, ArC), 136.7 (d, $^2J_{\text{CF}}$ 31.2, C5), 142.8 (d, $^3J_{\text{CF}}$ 9.6, C4), 148.6 (d, $^1J_{\text{CF}}$ 240.5, C6), 155.4 (s, ArC), 157.4 (s, ArC); δ_{F} (376MHz, CDCl_3) -97.2 (1F, s, F6); m/z (ES^+) 383 (45%, $[\text{M}+\text{H}]^+$), 340 (40, $[\text{M}+\text{MeCN-THP}]^+$), 299 (100, $[\text{M}+\text{H-THP}]^+$).

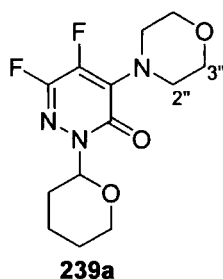
4,5-Bis(allyloxy)-6-fluoro-2-(tetrahydro-2H-pyran-2-yl)pyridazin-3(2H)-one 242c



A Greenhouse Plus tube was charged with 4,5,6-trifluoro-2-(tetrahydro-2H-pyran-2-yl)pyridazin-3(2H)-one (100mg, 0.427mmol), sodium hydride (0.034g, 60% dispersion in mineral oil, 0.854mmol) and dissolved in acetonitrile (5ml). Allyl alcohol (0.058ml, 0.854mmol) was added under an atmosphere of nitrogen, and the mixture stirred at room temperature for 20 hours. After this period the solvent was evaporated in a blowdown evaporator, before being redissolved in dichloromethane (5ml). Water (5ml) was added and the organic layer separated on a hydrophobic frit. The aqueous layer was washed with further portions of dichloromethane (3 × 5ml), and the organic extracts dried over MgSO_4 . After filtration and evaporation, the crude material was dissolved in 1ml DMSO / Methanol (1:1) and purified by mass directed automated purification. Residual TFA in the product was then removed by passing through an NH_2 functionalised SPE column, elution with methanol. After solvent evaporation, this yielded the major isomer *4,5-bis(allyloxy)-6-fluoro-2-(tetrahydro-2H-pyran-2-yl)pyridazin-3(2H)-one 242c* (0.046g, 35%) as a colourless oil; (Found $[\text{MH}]^+$ 311.1401. $\text{C}_{15}\text{H}_{19}\text{FN}_2\text{O}_4$ requires $[\text{MH}]^+$ 311.1407); δ_{H} (400MHz, CDCl_3) 1.54 (1H, m), 1.67 (1H, m), 2.01 (1H, m), 2.12 (1H, m), 3.70 (1H, td, $^2J_{\text{HH}}$ 11.3, $^3J_{\text{HH}}$ 2.5, C6'(H)), 4.10 (1H, ddd, $^2J_{\text{HH}}$ 11.3, $^3J_{\text{HH}}$ 2.3, $^3J_{\text{HH}}$ 2.0, C6'(H)), 4.79 (2H, d, $^3J_{\text{HH}}$ 5.8, $\text{OCH}_2\text{CH}=\text{CH}_2$), 4.87 (1H, ddd, $^3J_{\text{HH}}$ 12.6, $^3J_{\text{HH}}$ 6.0, $^2J_{\text{HH}}$ 1.3, $\text{OCH}_2\text{CH}=\text{CH}_2$),

4.95 (1H, ddd, $^3J_{\text{HH}}$ 12.6, $^3J_{\text{HH}}$ 5.8, $^2J_{\text{HH}}$ 1.3, $\text{OCH}_2\text{CH}=\text{CH}_2$), 5.29 (2H, ddd, $^3J_{\text{HH}}$ 7.6, $^4J_{\text{HH}}$ 1.3, $^4J_{\text{HH}}$ 1.3, $\text{OCH}_2\text{CH}=\text{CH}_2$), 5.36 (1H, dd, $^3J_{\text{HH}}$ 17.3, $^3J_{\text{HH}}$ 1.3, $^4J_{\text{HH}}$ 1.3, $\text{C}2'(\text{H})$), 5.99 (2H, m, $\text{OCH}_2\text{CH}=\text{CH}_2$); δ_{C} (100MHz, CDCl_3) 22.8 (s, CH_2), 24.8 (s, CH_2), 28.4 (s, CH_2), 68.7 (s, CH_2), 73.2 (s, CH_2), 82.5 (s, $\text{C}2'$), 119.3 (s, $\text{CH}=\text{CH}_2$), 119.6 (s, $\text{CH}=\text{CH}_2$), 132.0 (s, $\text{CH}=\text{CH}_2$), 132.7 (s, $\text{CH}=\text{CH}_2$), 138.4 (d, $^2J_{\text{CF}}$ 30.4, C5), 141.5 (d, $^3J_{\text{CF}}$ 8.8, C4), 149.1 (d, $^1J_{\text{CF}}$ 237.3, C6), 158.7 (s, C3); δ_{F} (376MHz, CDCl_3) -97.6 (1F, s, F6); m/z (ES^+) 310 (25%, $[\text{M}+\text{H}]^+$), 268 (17, $[\text{M}+\text{MeCN}-\text{THP}]^+$), 227 (100, $[\text{M}+\text{H}-\text{THP}]^+$).

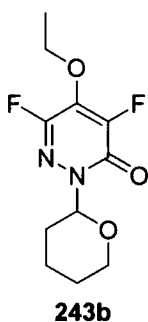
5,6-Difluoro-2-(tetrahydro-2H-pyran-2-yl)-4-morpholinopyridazin-3(2H)-one 239a



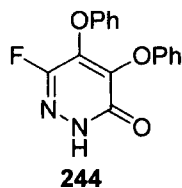
A clean, dry round-bottomed flask was charged with 4,5,6-trifluoro-2-(tetrahydro-2H-pyran-2-yl)pyridazin-3(2H)-one (0.10g, 0.427mmol) and dissolved in acetonitrile (5ml). The mixture was stirred under argon at room temperature for 16 hours. After this period the solvent was evaporated and the crude reaction mixture redissolved in dichloromethane (10ml). Water (10ml) was added and the organic layer separated. The aqueous layer was extracted with further portions of dichloromethane ($3 \times 10\text{ml}$), and the organic extracts dried over MgSO_4 . After filtration and evaporation, the crude material was purified by flash column chromatography (Hexane : ethyl acetate 4:1). This yielded the major isomer 5,6-difluoro-2-(tetrahydro-2H-pyran-2-yl)-4-morpholinopyridazin-3(2H)-one **239a** (0.075g, 58%) as a white solid; mp $86 - 87^\circ\text{C}$ (Found C, 51.6; H, 5.7; N, 13.6. $\text{C}_{13}\text{H}_{17}\text{F}_2\text{N}_3\text{O}_3$ requires C, 51.8; H, 5.7; N, 14.0%); δ_{H} (700MHz, CDCl_3) 1.53 (1H, d, $^2J_{\text{HH}}$ 8.9), 1.64 (3H, m), 2.01 (1H, m), 2.12 (1H, m), 3.56 (4H, t, $^3J_{\text{HH}}$ 4.8, $\text{C}2''(\text{H})$), 3.68 (1H, td, $^2J_{\text{HH}}$ 12.1, $^3J_{\text{HH}}$ 2.5, $\text{C}6'(\text{H})$), 3.78 (4H, t, $^3J_{\text{HH}}$ 4.8, $\text{C}3''(\text{H})$), 4.09 (1H, dd, $^2J_{\text{HH}}$ 12.1, $^3J_{\text{HH}}$ 4.2, $\text{C}6'(\text{H})$), 5.88 (1H, d, $^3J_{\text{HH}}$ 11.3, $\text{C}2'(\text{H})$); δ_{C} (100MHz, CDCl_3) 23.0 (s, CH_2), 25.0 (s, CH_2), 28.6 (s, CH_2), 49.8 (d, $^4J_{\text{CF}}$ 4.7, $\text{C}2''$), 67.4 (d, $^5J_{\text{CF}}$ 1.4, $\text{C}3''$), 69.0 (s, $\text{C}6'$), 83.5 (s, $\text{C}2'$), 134.3 (d, $^2J_{\text{CF}}$ 6.8, C5), 137.7 (dd, $^1J_{\text{CF}}$ 269.0, $^2J_{\text{CF}}$ 33.0, C4), 146.9 (dd, $^1J_{\text{CF}}$ 233.7,

$^2J_{CF}$ 19.2, C6), 159.2 (d, $^3J_{CF}$ 9.6, C3); δ_F (376MHz, $CDCl_3$) -104.7 (1F, d, $^3J_{FF}$ 28.2, F6), -147.1 (1F, d, $^3J_{FF}$ 28.2, F5); m/z (ES^+) 365 (100%, $[M+Na+MeCN]^+$).

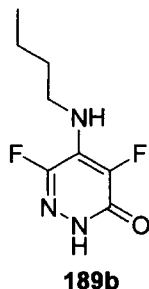
5-Ethoxy-4,6-difluoro-2-(tetrahydro-2H-pyran-2-yl)pyridazin-3(2H)-one 243b



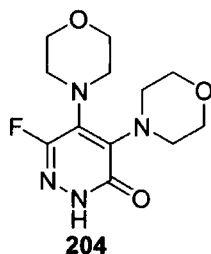
A clean, dry round-bottomed flask was charged with 4,5,6-trifluoro-2-(tetrahydro-2H-pyran-2-yl)pyridazin-3(2H)-one (0.25g, 1.07mmol) and sodium ethoxide (0.073g, 1.07mmol) and dissolved in ethanol (12.5ml). The mixture was stirred under argon at room temperature for 16 hours. After this period the solvent was evaporated and the crude reaction mixture redissolved in dichloromethane (20ml). Water (20ml) was added and the organic layer separated. The aqueous layer was extracted with further portions of dichloromethane (3×20 ml), and the organic extracts dried over $MgSO_4$. After filtration and evaporation, the crude material was purified by flash column chromatography (Hexane : ethyl acetate 4:1). This yielded the major isomer 5-ethoxy-4,6-difluoro-2-(tetrahydro-2H-pyran-2-yl)pyridazin-3(2H)-one **243b** (0.19g, 68%) as a white solid; mp 64 – 66°C (Found C, 50.5; H, 5.6; N, 10.4. $C_{11}H_{14}N_2F_2O_3$ requires C, 50.8; H, 5.4; N, 10.8%); ν_{max} / cm^{-1} 1007, 1031, 1080, 1166, 1185, 1379, 1442, 1586, 1660 (CO amide); δ_H (400MHz, $CDCl_3$) 1.38 (1H, td, $^2J_{HH}$ 7.1, $^3J_{HH}$ 3.2), 1.43 (3H, td, $^3J_{HH}$ 7.0, $^6J_{HF}$ 0.8, OCH_2CH_3), 1.55 (1H, m), 1.66 (3H, m), 3.71 (1H, td, $^2J_{HH}$ 11.6, $^3J_{HH}$ 2.6, C6'(H)), 4.08 (1H, dd, $^2J_{HH}$ 11.6, $^3J_{HH}$ 4.1, C6'(H)), 4.51 (2H, qd, $^3J_{HH}$ 7.0, $^5J_{HF}$ 3.1, OCH_2CH_3), 5.92 (1H, d, $^2J_{HH}$ 10.6, C2'(H)); δ_C (100MHz, $CDCl_3$) 15.2 (d, $^5J_{CF}$ 2.3, OCH_2CH_3), 22.6 (s, CH_2), 24.7 (s, CH_2), 28.3 (s, CH_2), 68.7 (s, C6'), 70.0 (d, $^4J_{CF}$ 7.9, OCH_2CH_3), 82.3 (dd, $^4J_{CF}$ 1.5, 1.5, C2'), 135.7 (dd, $^2J_{CF}$ 31.4, $^2J_{CF}$ 6.9, C5), 144.0 (dd, $^1J_{CF}$ 257.2, $^3J_{CF}$ 10.2, C4), 147.3 (dd, $^1J_{CF}$ 239.2, $^3J_{CF}$ 8.9, C6), 155.8 (d, $^2J_{CF}$ 22.6, C3); δ_F (376MHz, $CDCl_3$) -97.7 (1F, d, $^4J_{FF}$ 20.4, F6), -141.1 (1F, d, $^4J_{FF}$ 20.4, F4); m/z (ES^+) 324 (15%, $[M+Na+MeCN]^+$), 218 (68, $[M-THP+MeCN]^+$), 177 (79, $[M-THP+H]^+$).

6-Fluoro-4,5-diphenoxypyridazin-3(2H)-one 244

6-fluoro-2-(tetrahydro-2H-pyran-2-yl)-4,5-diphenoxypyridazin-3(2H)-one (0.047g, 0.131mmol) and *p*-toluenesulfonic acid (0.025g, 0.131mmol) were dissolved in distilled ethanol (10ml) under argon with stirring and heated to reflux for 8 hours, after which TLC suggested complete consumption of the starting material. The solvent was evaporated and the crude reaction mixture redissolved in dichloromethane (10ml) and water (10ml) and the organic layer separated. The aqueous layer was then extracted with further portions of dichloromethane (3 × 10ml) and the organic extracts were combined, dried (MgSO₄), filtered and evaporated *in vacuo* to provide a crude yellow material. This was purified by elution through a NH₂ functionalised solid phase extraction column with methanol to yield **6-fluoro-4,5-diphenoxypyridazin-3(2H)-one 244** (0.026g, 67%) as a white solid; mp 160 – 161°C (Found C, 64.1; H, 3.7; N, 9.1. C₁₆H₁₁N₂FO₃ requires C, 64.4; H, 3.7; N, 9.4%); ν_{max} / cm⁻¹ 1001, 1116, 1186, 1227, 1265, 1425, 1486, 1660 (CO amide), 2914 (br, NH); δ_{H} (500MHz, CDCl₃) 6.81 (2H, d, ³J_{HH} 8.9, ArH), 6.83 (2H, d, ³J_{HH} 9.3, ArH), 7.05 (1H, t, ³J_{HH} 7.4, ArH), 7.09 (1H, t, ³J_{HH} 8.3, ArH), 7.21 (2H, t, ³J_{HH} 8.3, ArH), 7.24 (2H, t, ³J_{HH} 9.7, ArH); δ_{C} (125MHz, CDCl₃) 116.6 (s, ArC), 116.6 (s, ArC), 124.3 (s, ArC), 124.7 (s, ArC), 129.6 (s ArC), 129.9 (s, ArC), 138.0 (d, ²J_{CF} 30.5, C5), 143.2 (d, ³J_{CF} 9.0, C4), 158.1 (d, ¹J_{CF} 240.0, C6), 155.4 (d, ⁴J_{CF} 1.4), 160.3 (s, ArC), 160.3 (s, ArC); δ_{F} (376MHz, CDCl₃) -98.4 (1F, s, F6); m/z (ES⁺) 619 (100%, [2M+Na]⁺), 362 (48, [M+Na+MeCN]⁺).

5-(Butylamino)-4,6-difluoropyridazin-3(2H)-one 189b

5-(Butylamino)-4,6-difluoro-2-(tetrahydro-2H-pyran-2-yl)pyridazin-3(2H)-one (0.020g, 0.070mmol) and *p*-toluenesulfonic acid (0.013g, 0.070mmol) were dissolved in distilled ethanol (10ml) under argon with stirring and heated to reflux for 8 hours, after which TLC suggested complete consumption of the starting material. The solvent was evaporated and the crude reaction mixture redissolved in dichloromethane (10ml) and water (10ml) and the organic layer separated. The aqueous layer was then extracted with further portions of dichloromethane (3 × 10ml) and the organic extracts were combined, dried (MgSO₄), filtered and evaporated *in vacuo* to provide a crude yellow material. This was purified by elution through silica gel with dichloromethane to yield 5-(butylamino)-4,6-difluoropyridazin-3(2H)-one **189b** (0.010g, 77%); data as previously.

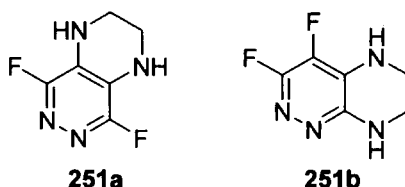
6-Fluoro-4,5-dimorpholinopyridazin-3(2H)-one 204

6-fluoro-2-(tetrahydro-2H-pyran-2-yl)-4,5-dimorpholinopyridazin-3(2H)-one (0.043g, 0.136mmol) and *p*-toluenesulfonic acid (0.026g, 0.136mmol) were dissolved in distilled ethanol (10ml) under argon with stirring and heated to reflux for 8 hours, after which TLC suggested complete consumption of the starting material. The solvent was evaporated and the crude reaction mixture redissolved in dichloromethane (10ml) and water (10ml) and the organic layer separated. The aqueous layer was then extracted with further portions of dichloromethane (3 × 10ml) and the organic extracts were combined, dried (MgSO₄), filtered and evaporated *in vacuo* to provide a crude yellow material. This was

purified by elution through silica gel with dichloromethane to yield *6-fluoro-4,5-dimorpholinopyridazin-3(2H)-one* **204** (0.028g, 72%); data as previously.

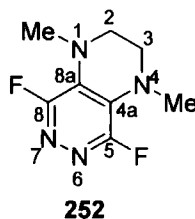
7.4 Experimental to Chapter 4

5,8-Difluoro-1,2,3,4-tetrahydropyrazino[2,3-d]pyridazine **251a** and *3,4-difluoro-5,6,7,8-tetrahydropyrazino[2,3-c]pyridazine* **251b**

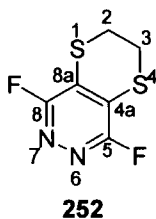


Tetrafluoropyridazine (0.60g, 3.96mmol) was dissolved in dry acetonitrile (100ml) under argon with stirring. Ethylenediamine (0.29ml, 4.4mmol) was added, and the mixture stirred at 80°C for 16 hours. The solution was then allowed to cool before the addition of water (50ml) and ethyl acetate (30ml). The organic phase was separated and the aqueous phase extracted with ethyl acetate (3 × 30ml). The combined organic extracts were dried (MgSO₄), filtered and evaporated *in vacuo* to yield a crude yellow product (0.46g). This contained 2 isomers in the ratio 86 : 14. The crude material was then recrystallised from ethyl acetate to yield *5,8-difluoro-1,2,3,4-tetrahydropyrazino[2,3-d]pyridazine* **251a** (0.18g, 26%) as a yellow-cream solid; mp 192 – 194°C (Found C, 41.9; H, 3.7%; N, 32.5. C₆H₆N₄F₂ requires C, 41.9; H, 3.5; N, 32.6%); δ_{H} (400MHz, CDCl₃) 3.55 (4H, s, CH₂CH₂), 4.36 (2H, br s, 2 × NH); δ_{F} (376MHz, CDCl₃) -103.9 (2F, s); m/z (EI⁺) 172 (79%, [M]), 171 (100, [M-H]⁺), 70 (21, [C₃H₆N₂]⁺), 30 (22), 28 (32, [N₂]⁺).

The minor isomer *3,4-difluoro-5,6,7,8-tetrahydropyrazino[2,3-c]pyridazine* **251b** was not isolated. δ_{F} (400MHz, CDCl₃) -92.3 (1F, s), -155.0 (1F, s); m/z (EI⁺) 172 (100% [M⁺]), 171 (86, [M-H]⁺), 116 (25), 89 (28), 70 (56, [C₃H₆N₂]⁺), 30 (49), 28 (51, [N₂]⁺).

5,8-Difluoro-1,2,3,4-tetrahydro-1,4-dimethylpyrazino-[2,3-d]pyridazine 252

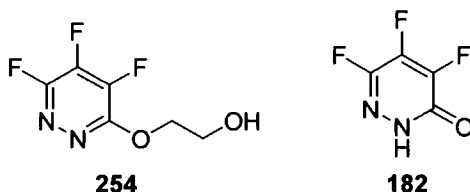
Tetrafluoropyridazine (0.60g, 3.96mmol) was dissolved in dry acetonitrile (100ml) under argon with stirring. N,N'-Dimethylethylenediamine (0.47ml, 4.4mmol) and sodium hydrogencarbonate (1.33g, 15.8mmol) were added, and the mixture stirred for 4 hours. Water (50ml) was added to quench the reaction, followed by ethyl acetate (30ml). The organic phase was separated and the aqueous phase extracted with ethyl acetate (3 × 30ml). The combined organic extracts were dried (MgSO₄), filtered and evaporated *in vacuo* to yield a crude yellow product (0.61g), which was purified by flash column chromatography (elutant ethyl acetate / hexane 1:1) to yield pure 5,8-difluoro-1,2,3,4-tetrahydro-1,4-dimethylpyrazino-[2,3-d]pyridazine **252** (0.62g, 91%) as white crystals; mp 169 – 171°C (Found C, 47.9; H, 5.0; N, 27.8.; C₈H₁₀N₄F₂ requires C, 48.0; H, 5.0; N, 28.0%); ν_{\max} / cm⁻¹ 1092, 1159, 1251, 1343, 1410, 1557, 2900 (CH); δ_{H} (400MHz, CDCl₃) 3.05 (6H, t, ⁵J_{HF} 1.9, CH₃), 3.20 (4H, s, CH₂CH₂); δ_{C} (100MHz, CDCl₃) 42.2 (dd, ⁴J_{CF} 6.0, C2/3), 48.4 (s, 2 × CH₃), 125.8 (t, ²J_{CF} 16.7, C4a,8a), 156.2 (dd, ¹J_{CF} 235.2, ⁴J_{CF} 3.8, C5,8); δ_{F} (376MHz, CDCl₃) -92.1 (2F, s); *m/z* (EI⁺) 200 (100%, [M]⁺), 185 (42, [M-Me]⁺), 156 (20), 42 (76).

5,8-Difluoro-2,3-dihydro-[1,4]dithiino[2,3-d]pyridazine 253

Tetrafluoropyridazine (0.25g, 1.64mmol) was dissolved in dry acetonitrile (20ml) and 1,2-ethanedithiol (0.15ml, 1.81mmol) and sodium hydrogen carbonate (0.28g, 3.29mmol) were added. The mixture was allowed to stir at room temperature for 2 hours before the solvent was evaporated, and the crude reaction mixture redissolved in dichloromethane (20ml) and water (20ml). The aqueous layer was separated before extraction with further portions of dichloromethane (3 × 20ml). The combined organic

extracts were then dried (MgSO_4), filtered and evaporated *in vacuo* to provide a crude yellow material which was purified by recrystallisation from acetonitrile to yield 5,8-difluoro-2,3-dihydro-[1,4]dithiino[2,3-d]pyridazine **253** as a white solid (0.29g, 85%); mp $123 - 125^\circ\text{C}$ (Found C, 34.3; H, 3.2; N, 13.7; $\text{C}_6\text{H}_4\text{N}_2\text{F}_2\text{S}_2$ requires C, 34.9; H, 2.0; N, 13.6%); δ_{H} (700MHz, CDCl_3) 3.41 (4H, s, CH_2CH_2); δ_{C} (175MHz, CDCl_3) 25.5 (s, C2/3), 126.0 (dd, $^2J_{\text{CF}}$ 20.0, C4a,8a), 160.0 (dd, $^1J_{\text{CF}}$ 242.2, $^4J_{\text{CF}}$ 5.1, C5,8); δ_{F} (658MHz, CDCl_3) -84.8 (2F, s); m/z (EI) 206 (88%, $[\text{M}]^+$), 191 (100), 178 (19, $[\text{M}-\text{N}_2]^+$), 132 (19), 87 (29).

2-(4,5,6-Trifluoropyridazin-3-yloxy)ethanol **254** and 4,5,6-trifluoropyridazin-3(2H)-one **182**

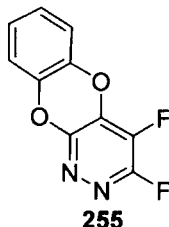


Tetrafluoropyridazine (0.5g, 3.29mmol) was dissolved in concentrated sulfuric acid (10ml) at 0°C and ethylene glycol (2.5ml) was added dropwise over 30 minutes. The mixture was stirred at 0°C for 1 hour before the addition of diethyl ether (50ml) and the reaction mixture was poured onto ice (100g). The organic layer was separated, and the aqueous layer was extracted with further portions of diethyl ether ($2 \times 50\text{ml}$). The organic extracts were combined, dried (MgSO_4), filtered and evaporated *in vacuo* to provide a crude yellow material. This was then purified by flash column chromatography using hexane and dichloromethane (4:1) as elutant to yield 2-(4,5,6-trifluoropyridazin-3-yloxy)ethanol **254** (0.16g, 25%) as a colourless oil; (Found C, 37.2; H, 2.4; N, 14.7. $\text{C}_6\text{H}_5\text{N}_2\text{F}_3\text{O}_2$ requires C, 37.1; H, 2.6; N, 14.4%); δ_{H} (300MHz, CDCl_3) 2.39 (1H, br s, OH), 4.04 (2H, m, $\text{ArOCH}_2\text{CH}_2\text{OH}$), 4.69 (2H, m, $\text{ArOCH}_2\text{CH}_2\text{OH}$); δ_{F} (282MHz, CDCl_3) -97.7 (1F, dd, $^3J_{\text{FF}}$ 26.1, $^4J_{\text{FF}}$ 20.3, F6), 146.3 (1F, dd, $^3J_{\text{FF}}$ 15.9, $^4J_{\text{FF}}$ 20.3, F4), 151.9 (1F, dd, $^3J_{\text{FF}}$ 26.1, $^3J_{\text{FF}}$ 15.9, F5); m/z (ES^+) 195 (100%, $[\text{M}+\text{H}]^+$).

Also produced was 4,5,6-trifluoropyridazin-3(2H)-one **182** (0.15g, 30%) as white crystals; δ_{F} (282MHz, CDCl_3) -101.7 (1F, dd, $^3J_{\text{FF}}$ 25.7, $^4J_{\text{FF}}$ 16.2, F6), -136.9 (1F, dd, $^3J_{\text{FF}}$ 15.5, $^4J_{\text{FF}}$ 16.2, F4), -143.5 (1F, dd, $^3J_{\text{FF}}$ 25.7, $^3J_{\text{FF}}$ 15.5, F5); δ_{H} (300MHz, CDCl_3) 11.8 – 11.4 (1H, br s, NH); m/z (EI^+) 151 (5%, $[\text{M}]^+$), 150 (97, $[\text{M}-\text{H}]^+$), 122 (25), 121 (21), 93

(100), 74 (68), 31 (100, $[\text{CF}]^+$). Spectral data was in agreement with a known sample of this compound.

3,4-Difluoro-9,10-dioxo-1,2-diaza-anthracene 255



METHOD A:

Catechol (0.362g, 3.29mmol) was dissolved in dry THF (20ml) under argon with stirring, and the solution was cooled to -78°C . $n\text{-BuLi}$ (1.6M in hexanes, 4.11ml, 6.58mmol) was added dropwise, and the solution allowed to stir for 30 minutes. After this period tetrafluoropyridazine (0.5g, 3.29mmol) was added and the mixture was allowed to slowly warm to room temperature and stirred for 16 hours. Then the reaction was quenched by the addition of water (20ml), followed by ethyl acetate (20ml). The aqueous layer was separated, then extracted with further portions of ethyl acetate ($2 \times 20\text{ml}$). The combined organic extracts were then dried (MgSO_4), filtered and evaporated to yield a crude brown solid (0.61g). This was then purified by flash column chromatography (elutant = hexane and dichloromethane 10:1 (600ml), followed by 4:1 (300ml) to yield pure *4a,9a-Dihydro-9,10-dioxo-1,2-diaza-anthracene 255* (0.43g, 59%) as a white solid; mp $146 - 148^{\circ}\text{C}$ (Found C, 54.0; H, 1.9; N, 12.6. $\text{C}_8\text{H}_{11}\text{N}_4\text{FO}$ requires C, 54.1; H, 1.8; N, 12.6%); $\nu_{\text{max}} / \text{cm}^{-1}$ 1015, 1035, 1094, 1115 (C-O), 1260 (C-O), 1416, 1464, 1490, 1568, 1654; δ_{H} (400MHz, CDCl_3) 7.13 – 7.06 (m, 4H, ArH); δ_{C} (100MHz, CDCl_3) 117.0 (s), 118.1 (s), 126.0 (s), 126.8 (s), 127.0 (s), 133.4 (t, J_{CF} 6.3), 136.8 (dd, $^1J_{\text{CF}}$ 283.7, $^2J_{\text{CF}}$ 32.0), 139.5 (d, $^1J_{\text{CF}}$ 173.1), 154.5 (s), 156.9 (d, J_{CF} 9.8); δ_{F} (376MHz, CDCl_3) -96.4 (1F, d, $^3J_{\text{FF}}$ 25.8), -151.9 (1F, d, $^3J_{\text{FF}}$ 25.9); m/z (EI^+) 222 (10%, $[\text{M}^+]$), 138 (43), 74 (66), 63 (67), 62 (62), 50 (100).

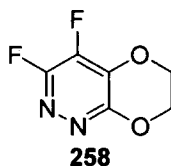
Minor column fraction contained several products (not isolated separately) including *4-butyl-3,5,6-trifluoropyridazine 256*; δ_{F} (282MHz, CDCl_3) -81.6 (1F, dd, $^3J_{\text{FF}}$ 33.4, $^5J_{\text{FF}}$ 22.0), -98.9 (1F, dd, $^3J_{\text{FF}}$ 34.2), -129.2 (1F, dd, $^3J_{\text{FF}}$ 27.8, $^4J_{\text{FF}}$ 23.7); m/z (EI^+) 190 (38%, $[\text{M}^+]$), 148 (42, $[\text{M-Pr}]^+$), 43 (100, $[\text{C}_3\text{H}_7]^+$), 41 (77); Also, *4,5-dibutyl-3,6-*

difluoropyridazine 257; δ_F (282MHz, $CDCl_3$) -87.5 (1F, s); m/z (EI^+) 228 (29%, $[M^+]$), 171 (14, $[M-Bu]^+$), 157 (27), 144 (48), 43 (100, $[C_3H_7]^+$), 41 (57). Also unidentified product; δ_F (282MHz, $CDCl_3$) -88.2 (1F, t, $^3J_{FF}$ 28.4), -96.2 (1F, dd, $^3J_{FF}$ 31.8, $^4J_{FF}$ 24.2), -148.1 (1F, t, $^3J_{FF}$ 24.9); m/z (EI^+) 206.

METHOD B:

Catechol (0.80g, 7.23mmol) was dissolved in tetrahydrofuran at 0°C under argon with stirring and added to sodium hydride (0.35g, 14.5mmol, 60% dispersion in mineral oil). Tetrafluoropyridazine (1.00g, 6.58mmol) was added dropwise and the mixture stirred at 0°C for 8 hours. After this period the solvent was evaporated, and the crude material redissolved in dichloromethane (25ml) and water (25ml). The organic layer was separated and the aqueous layer washed with further portions of dichloromethane (3 × 25ml). The combined organic extracts were then dried ($MgSO_4$), filtered and evaporated *in vacuo* to provide a crude yellow material which was purified by recrystallisation from acetonitrile to yield *4a,9a-Dihydro-9,10-dioxo-1,2-diaza-anthracene 255* (1.09g, 75%), data as previously.

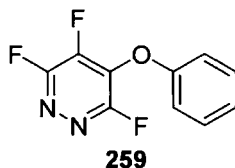
3,4-Difluoro-6,7-dihydro-[1,4]dioxino[2,3-c]pyridazine 258



Ethylene Glycol (0.18g, 3.29mmol) was dissolved in dry THF (20ml) under argon with stirring, and the solution was cooled to -78°C. *n*-BuLi (1.6M in hexanes, 4.11ml, 6.58mmol) was added dropwise, and the solution allowed to stir for 30 minutes. After this period tetrafluoropyridazine (0.5g, 3.29mmol) was added and the mixture was allowed to slowly warm to room temperature and stirred for 16 hours. Then the reaction was quenched by the addition of water (20ml), followed by ethyl acetate (20ml). The aqueous layer was separated, then extracted with further portions of ethyl acetate (2 × 20ml). The combined organic extracts were then dried ($MgSO_4$), filtered and evaporated to yield a crude cream solid (0.61g). This contained *3,4-difluoro-6,7-dihydro-[1,4]dioxino[2,3-c]pyridazine*, which was not purified; δ_H (400MHz, $CDCl_3$) 4.46 (2H, t, $^3J_{HH}$ 6.2, CH_2),

4.54 (2H, t, $^3J_{\text{HH}}$ 6.2, CH₂); δ_{F} (376MHz, CDCl₃) -101.4 (1F, d, $^3J_{\text{FF}}$ 26.4, F3), -154.5 (1F, d, $^3J_{\text{FF}}$ 26.4, F4); m/z (EI) 174 (12%, [M]⁺), 90 (71), 62 (100).

3,4,6-Trifluoro-5-phenoxy pyridazine **259**



Phenol (0.17g, 1.81mmol) was dissolved in tetrahydrofuran (20ml) and sodium hydride (0.072g, 1.81mmol, 60% dispersion in mineral oil) was added at 0°C with stirring. Tetrafluoropyridazine (0.25g, 1.64mmol) was added dropwise, and the mixture stirred at 0°C for 8 hours. After this period the solvent was evaporated, and the crude material redissolved in dichloromethane (25ml) and water (25ml). The organic layer was separated and the aqueous layer washed with further portions of dichloromethane (3 × 25ml). The combined organic extracts were then dried (MgSO₄), filtered and evaporated *in vacuo* to provide a crude yellow material which was purified by flash column chromatography (elutant hexane : ethyl acetate 4:1) to yield 3,4,6-trifluoro-5-phenoxy pyridazine **259** (0.25g, 68%) as a colourless oil; (Found C, 53.2; H, 2.5; N, 12.2. C₁₀H₅N₂F₃O requires C, 53.1; H, 2.2; N, 12.4%); δ_{H} (200MHz, CDCl₃) 7.04 – 7.42 (6H, m, ArH); δ_{F} (188MHz, CDCl₃) -86.2 (1F, dd, $^5J_{\text{FF}}$ 31.2, $^3/4J_{\text{FF}}$ 23.7, F3/6), -94.5 (1F, dd, $^5J_{\text{FF}}$ 31.2, $^3/4J_{\text{FF}}$ 23.7, F3/6), -140.4 (1F, dd, $^3J_{\text{FF}}$ 23.7, $^4J_{\text{FF}}$ 23.7, F4); m/z (ES⁺) 227 (100%, [M+H]⁺).

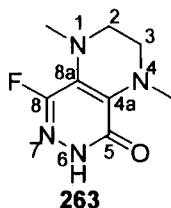
5,8-Difluoro-1,2,3,4-tetrahydro-1,4-dimethylpyrazino[2,3-d]pyridazine **252**



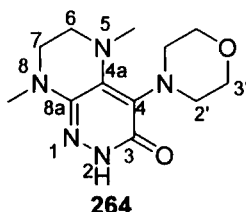
N,N'-dimethylethylenediamine (0.71ml, 6.58mmol) was dissolved in dry THF (20ml) under argon with stirring, and the solution was cooled to -78°C. n-BuLi (1.6M in hexanes, 8.22ml, 6.58mmol) was added dropwise, and the solution allowed to stir for 30

minutes. After this period tetrafluoropyridazine (1.00g, 6.58mmol) was added and the mixture was allowed to slowly warm to room temperature and stirred for 16 hours. Then the reaction was quenched by the addition of water (20ml), followed by ethyl acetate (20ml). The aqueous layer was separated, then extracted with further portions of ethyl acetate (2 × 20ml). The combined organic extracts were then dried (MgSO₄), filtered and evaporated to yield a crude brown solid (0.61g). This was then purified by flash column chromatography (elutant = hexane and ethyl acetate, 4:1) to yield 5,8-difluoro-1,2,3,4-tetrahydro-1,4-dimethylpyrazino[2,3-d]pyridazine **252** (0.95g, 72%); data as previously.

8-Fluoro-1,2,3,4-tetrahydro-1,4-dimethylpyrazino[2,3-d]pyridazin-5(6H)-one **263**

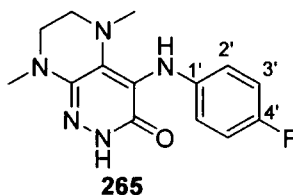


4,5,6-Trifluoropyridazin-3(2*H*)-one (1.00g, 6.67mmol) was dissolved in acetonitrile (50ml) under argon with stirring. *N,N'*-dimethylethylenediamine (1.43ml, 13.3mmol) was added dropwise and the mixture stirred at room temperature for 16 hours. After this period the solvent was evaporated, and the crude material redissolved in dichloromethane (50ml) and water (50ml). The aqueous layer was separated and washed with further portions of dichloromethane (3 × 25ml). The combined organic extracts were dried (MgSO₄), filtered and evaporated *in vacuo* to yield a crude yellow product (1.08g), which was purified by recrystallisation from acetonitrile to yield 8-fluoro-1,2,3,4-tetrahydro-1,4-dimethylpyrazino[2,3-d]pyridazin-5(6*H*)-one **263** (1.08g, 82%) as a white solid; mp 159 – 161°C (Found C, 48.4; H, 5.7; N, 28.6. C₈H₁₁N₄FO requires C, 48.5; H, 5.6; N, 28.3%); δ_H (400MHz, CDCl₃) 2.84 (3H, t, ⁵J_{HF} 1.7, N1(CH₃)), 2.94 (2H, m, CH₂), 3.00 (2H, m, CH₂), 3.18 (3H, s, N4(CH₃)), 11.01 (1H, br s, ring NH); δ_C (100MHz, CDCl₃) 31.1 (N4(CH₃)), 40.9 (s, C3), 43.1 (d, ⁴J_{CF} 9.1, N1(CH₃)), 47.5 (d, ⁴J_{CF} 6.7, C2), 124.7 (d, ²J_{CF} 27.2, C8a), 132.6 (d, ³J_{CF} 9.7, C4a), 150.4 (d, ¹J_{CF} 230.4, C8), 159.1 (s, C5); δ_F (376MHz, CDCl₃) -97.6 (1F, s); *m/z* (EI⁺) 198 (100%, [M⁺]), 183 (29, [M – Me]⁺), 169 (28), 168 (27, [M – 2Me]⁺), 42 (46).

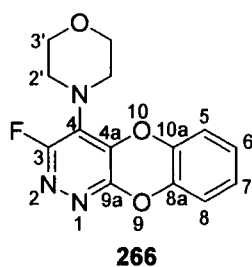
5,6,7,8-Tetrahydro-5,8-dimethyl-4-morpholinopyrazino[2,3-*c*]pyridazin-3(2H)-one 264

A 2-5ml microwave vial was charged with 5,6-difluoro-4-morpholinopyridazin-3(2H)-one (0.25g, 1.15mmol) and N,N'-dimethylethylenediamine (0.25ml, 2.30mmol) and dissolved in dry acetonitrile (3ml). The mixture was irradiated at 150°C for 20 minutes, after which TLC indicated complete conversion of starting material. Water (5ml) and dichloromethane (10ml) were added and the layers separated. The aqueous layer was washed with a further 2 portions of dichloromethane (2 × 10ml), before the combined organic extracts were dried (MgSO₄), filtered and evaporated *in vacuo* to yield a crude yellow material. This was recrystallised from acetonitrile to yield 5,6,7,8-tetrahydro-5,8-dimethyl-4-morpholinopyrazino[2,3-*c*]pyridazin-3(2H)-one **264** (0.24g, 79%) as white crystals; mp > 250°C; (Found C, 54.1; H, 7.2; N, 26.3. C₁₂H₁₉N₅O₂ requires C, 54.3; H, 7.2; N, 26.4%); ν_{max} / cm⁻¹ 981, 1108, 1193, 1258, 1367, 1407, 1492, 1611 (CO amide), 2956 (br, NH); δ_{H} (400MHz, CDCl₃) 2.83 (3H, s, CH₃), 3.17 (2H, t, ³J_{HH} 4.8, C(6/7)H₂), 3.24 (4H, t, ³J_{HH} 4.7, C2'(H)), 3.30 (3H, s, CH₃), 3.38 (2H, t, ³J_{HH} 4.8, C(6/7)H₂), 3.75 (4H, t, ³J_{HH} 4.7, C3'(H)), 9.14 (1H, br s, ring NH). δ_{C} (100MHz, CDCl₃) 37.6 (s, CH₃), 42.2 (s, CH₃), 47.1 (s, C6/7), 49.5 (s, C2'), 51.6 (s, C6/7), 67.1 (s, C3'), 124.1 (s, ArC), 137.9 (s, ArC), 144.3 (s, C8a), 161.3 (s, C3); m/z (ES⁺) 266 (100%, [M+H]⁺).

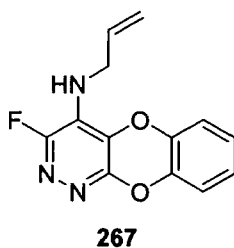
4-(4-Fluoro-phenylamino)-5,6,7,8-tetrahydro-5,8-dimethylpyrazino[2,3-*c*]pyridazin-3(2*H*)-one 265



A 0.5-2ml microwave vial was charged with 4-(4-fluorophenylamino)-5,6-difluoropyridazin-3(2*H*)-one (0.10g, 0.415mmol) and *N,N'*-dimethylethylenediamine (0.11ml, 1.04mmol) and dissolved in dry acetonitrile (1ml). The mixture was irradiated at 150°C for 30 minutes, after which TLC indicated complete conversion of starting material. Water (5ml) and dichloromethane (10ml) were added and the layers separated. The aqueous layer was washed with a further 2 portions of dichloromethane (2 × 10ml), before the combined organic extracts were dried (MgSO₄), filtered and evaporated *in vacuo* to yield a crude yellow material. This was recrystallised from acetonitrile to yield 4-(4-fluorophenylamino)-5,6,7,8-tetrahydro-5,8-dimethylpyrazino[2,3-*c*]pyridazin-3(2*H*)-one **265** (0.08g, 67%) as white crystals; mp > 250°C (Found C, 58.3; H, 5.7; N, 24.2. C₁₄H₁₆N₅OF requires C, 58.1; H, 5.6; N, 24.2%); δ_H (700MHz, CDCl₃) 2.52 (3H, s, CH₃), 2.91 (3H, s, CH₃), 3.28 (2H, t, ³J_{HH} 6.1, C(6/7)H₂), 3.38 (2H, t, ³J_{HH} 6.1, C(6/7)H₂), 6.65 (2H, m, C2'(H)), 6.80 (1H, br s, NHAr), 6.89 (2H, m, C3'(H)), 11.09 (1H, br s, ring NH). δ_C (175MHz, CDCl₃) 37.2 (s, CH₃), 37.3 (s, CH₃), 47.5 (s, C6/7), 51.2 (s, C6/7), 114.9 (d, ²J_{CF} 22.5, C3'), 117.9 (s, ArC), 118.1 (d, ³J_{CF} 7.7, C2'), 127.9 (s, ArC), 137.4 (s, ArC), 145.3 (s, ArC), 157.4 (d, ¹J_{CF} 238.5, C4'), 160.0 (s, C3); δ_F (658MHz, CDCl₃) -124.6 (1F, m); *m/z* (ES⁺) 290 (100%, [M+H]⁺).

3-Fluoro-4-morpholin-4-yl-9,10-dioxo-1,2-diaza-anthracene 266

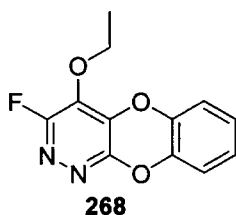
3,4-Difluoro-9,10-dioxo-1,2-diaza-anthracene (0.20g, 0.900mmol) was dissolved in dry acetonitrile (2ml) in a 0.5-2ml microwave vial and morpholine (0.16ml, 1.80mmol) was added. The vial was sealed under argon and irradiated at 150°C for 20 minutes, after which dichloromethane (20ml) and water (20ml) were added and the organic layer separated. The aqueous layer was then washed with further portions of dichloromethane (3 × 20ml) to give a crude yellow material which was purified by flash column chromatography (elutant hexane : ethyl acetate 2:1) to yield **3-Fluoro-4-morpholin-4-yl-9,10-dioxo-1,2-diaza-anthracene 266** (0.18g, 71%) as white crystals; mp 207 – 208°C (Found $[MH]^+$ 290.09345. $C_{14}H_{12}FN_3O_3$ requires $[MH]^+$ 290.09355); δ_H (700MHz, $CDCl_3$) 3.44 (4H, t, $^3J_{HH}$ 4.4, C2'(H)), 3.84 (4H, t, $^3J_{HH}$ 4.4, C3'(H)), 6.94 (1H, d, $^3J_{HH}$ 7.6, ArH), 7.01 (1H, tm, $^3J_{HH}$ 7.6, ArH), 7.06 (2H, m, ArH); δ_C (175MHz, $CDCl_3$) 50.4 (d, $^4J_{CF}$ 4.0, C2'), 67.3 (s, C3'), 116.5 (s, ArC), 117.7 (s, ArC), 125.2 (s, ArC), 125.9 (s, ArC), 126.0 (d, $^2J_{CF}$ 25.4, C4), 134.6 (d, $^3J_{CF}$ 8.9, C4a), 139.4 (s, ArC), 140.9 (s, ArC), 153.7 (s, ArC), 159.0 (d, $^1J_{CF}$ 237.7, C3); δ_F (658MHz, $CDCl_3$) -86.4 (1F, s); m/z (ES^+) 290 (100%, $[M+H]^+$).

3-Fluoro-4-allylamino-9,10-dioxo-1,2-diaza-anthracene 267

3,4-Difluoro-9,10-dioxo-1,2-diaza-anthracene (0.15g, 0.675mmol) was dissolved in dry acetonitrile (2ml) in a 0.5-2ml microwave vial and allylamine (0.10ml, 1.35mmol) was

added. The vial was sealed under argon and irradiated at 150°C for 20 minutes, after which dichloromethane (20ml) and water (20ml) were added and the organic layer separated. The aqueous layer was then washed with further portions of dichloromethane (3 × 20ml) to give a crude yellow material which was purified by flash column chromatography (elutant hexane : ethyl acetate 2:1) to yield *3-Fluoro-4-allylamino-9,10-dioxo-1,2-diaza-anthracene* **267** (0.14g, 80%) as white crystals; mp 175 – 177°C (Found C, 60.3; H, 4.0; N, 16.3. C₁₃H₁₀N₃FO₂ requires C, 60.2; H, 3.9; N, 16.2%); δ_{H} (500MHz, DMSO-d₆) 4.04 (2H, t, $^3J_{\text{HH}}$ 5.1, NHCH₂CH=CH₂), 5.10 (1H, dd, $^3J_{\text{HH}}$ 10.3, $^2J_{\text{HH}}$ 1.5, NHCH₂CH=CH₂), 5.17 (1H, dd, $^3J_{\text{HH}}$ 17.2, $^2J_{\text{HH}}$ 1.5, NHCH₂CH=CH₂), 5.94 (1H, ddt, $^3J_{\text{HH}}$ 17.2, 10.2, 5.1, NHCH₂CH=CH₂), 6.96 (1H, br t, $^3J_{\text{HH}}$ 5.1, NHCH₂CH=CH₂), 7.07 (3H, m, ArH), 7.12 (1H, m, ArH); δ_{C} (125MHz, DMSO-d₆) 45.7 (d, $^4J_{\text{CF}}$ 2.5, NHCH₂CH=CH₂), 115.3 (s), 116.4 (s), 124.6 (d, $^2J_{\text{CF}}$ 28.2, C4), 125.1 (s), 125.2 (s), 127.2 (d, $^3J_{\text{CF}}$ 9.6, C4a), 136.1 (s), 139.4 (s), 140.5 (s), 152.3 (s), 155.2 (d, $^1J_{\text{CF}}$ 230.4, C3); δ_{F} (470MHz, DMSO-d₆) -93.7 (1F, s, F3); m/z (ES⁺) 323 (100%, [M+MeCN+Na]⁺), 260 (68, [M+H]⁺), 219 (69, [M+H-CH₂CH=CH₂]).

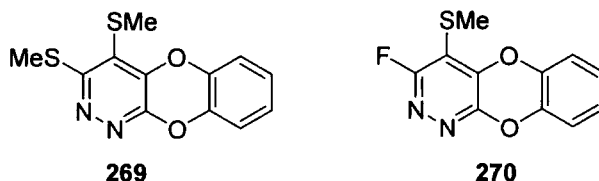
3-Fluoro-4-ethoxy-9,10-dioxo-1,2-diaza-anthracene **268**



3,4-Difluoro-9,10-dioxo-1,2-diaza-anthracene (0.10g, 0.45mmol) and sodium ethoxide (0.061g, 0.90mmol) were dissolved in dry ethanol (2ml) in a 0.5-2ml microwave vial. The vial was sealed under argon and irradiated at 150°C for 20 minutes, after which dichloromethane (20ml) and water (20ml) were added and the organic layer separated. The aqueous layer was then washed with further portions of dichloromethane (3 × 20ml) to give a crude yellow material which was purified by flash column chromatography (elutant hexane : ethyl acetate 2:1) to yield *3-Fluoro-4-ethoxy-9,10-dioxo-1,2-diaza-anthracene* **268** (0.074g, 66%), as white crystals, mp 131 – 133°C (Found C, 58.0; H, 3.7; N, 11.2. C₁₃H₁₀N₃FO₂ requires C, 58.1; H, 3.7; N, 11.3%); δ_{H} (500MHz, CDCl₃) 1.49 (3H, t, $^3J_{\text{HH}}$ 7.0, OCH₂CH₃), 4.52 (2H, qd, $^3J_{\text{HH}}$ 7.0, $^5J_{\text{HF}}$ 1.4, OCH₂CH₃), 7.00 – 7.11 (4H, m, ArH); δ_{C} (125MHz, DMSO-d₆) 15.7 (s, OCH₂CH₃), 70.6 (d, $^4J_{\text{CF}}$ 3.9, OCH₂CH₃), 116.7 (s, ArC),

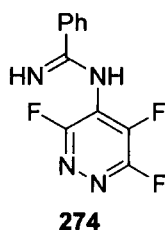
117.8 (s, ArC), 125.4 (s, ArC), 126.1 (s, ArC), 133.6 (d, $^2J_{CF}$ 27.2, C4), 135.1 (d, $^3J_{CF}$ 8.2, C4a), 139.2 (s, ArC), 140.7 (s, ArC), 154.0 (d, $^4J_{CF}$ 1.5, C9a), 158.2 (d, $^1J_{CF}$ 239.5, C3); δ_F (470MHz, $CDCl_3$) -92.4 (1F, s, F3); m/z (ES^+) 249 (100%, $[M+H]^+$)

3-Fluoro-4-methylthio-9,10-dioxo-1,2-diaza-anthracene **270** and *3,4-bis(methylthio)-9,10-dioxo-1,2-diaza-anthracene* **269**



3,4-Difluoro-9,10-dioxo-1,2-diaza-anthracene (0.10g, 0.45mmol) and sodium thiomethoxide (0.063g, 0.90mmol) were dissolved in dry acetonitrile (2ml) in a 0.5-2ml microwave vial. The vial was sealed under argon and irradiated at 150°C for 20 minutes, after which dichloromethane (20ml) and water (20ml) were added and the organic layer separated. The aqueous layer was then washed with further portions of dichloromethane (3 × 20ml) to give a crude yellow material which could not be separated by flash column chromatography (elutant hexane : ethyl acetate 2:1). The mixture contained *3-Fluoro-4-methylthio-9,10-dioxo-1,2-diaza-anthracene* **270**; δ_H (400MHz, $CDCl_3$) 2.47 (3H, s, CH_3), 7.00 – 7.10 (4H, ArH); δ_F (376MHz, $CDCl_3$) -78.8 (1F, s); m/z (ES^+) 251 (100%, $[M+H]^+$); and also contained *3,4-bis(methylthio)-9,10-dioxo-1,2-diaza-anthracene* **269**; δ_H (400MHz, $CDCl_3$) 3.57 (3H, s, CH_3), 2.62 (3H, s, CH_3), 7.00 – 7.18 (4H, ArH); m/z (ES^+) 279 (100%, $[M+H]^+$).

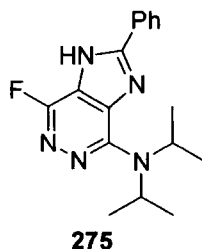
N-(3,5,6-Trifluoropyridazin-4-yl)benzamidinium **274**



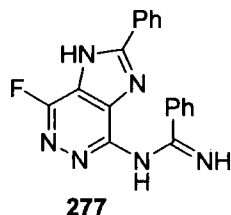
Tetrafluoropyridazine (0.60g, 3.96mmol) was mixed with benzamidinium hydrochloride (0.68g, 4.35mmol) and sodium hydrogen carbonate (1.32g, 15.8mmol) in acetonitrile (100ml). The resultant mixture was heated to 80°C under argon with stirring for 16 hours. After this period, the solvent was evaporated, and the residue dissolved in

ethyl acetate (50ml). This was washed with water (25ml) and the aqueous layer extracted with ethyl acetate (2×25 ml). The combined organic extracts were dried (MgSO_4), filtered and evaporated *in vacuo* to yield a crude brown material (0.81g), which was purified by recrystallisation from ethyl acetate and hexane (1:1) to yield *N*-(3,5,6-trifluoropyridazin-4-yl)benzamidine **274** (0.76g, 75%) as a yellow solid; mp $139 - 141^\circ\text{C}$ (Found $[\text{MH}]^+$ 253.06956. $\text{C}_{11}\text{H}_7\text{F}_3\text{N}_4$ requires $[\text{MH}]^+$ 253.06956); δ_{H} (700MHz, CDCl_3) 7.41 (1H, br s, NH), 7.48 (2H, t, $^3J_{\text{HH}}$ 7.2, C3'(H)), 7.56 (1H, t, $^3J_{\text{HH}}$ 7.2, C4'(H)), 7.93 (2H, d, $^3J_{\text{HH}}$ 7.2, C2'(H)), 8.08 (1H, br s, NH); δ_{C} (175MHz, DMSO-d_6) 127.6 (s, ArC), 128.4 (s, ArC), 131.4 (dd, $^2J_{\text{CF}}$ 31.4, 10.4, C4), 131.6 (s, ArC), 133.4 (s, ArC), 141.9 (ddd, $^1J_{\text{CF}}$ 269.1, $^2J_{\text{CF}}$ 26.8, $^3J_{\text{CF}}$ 9.3, C5), 156.2 (dd, $^1J_{\text{CF}}$ 235.8, $^2J_{\text{CF}}$ 11.4, C6), 159.5 (s, ArC), 160.6 (d, $^1J_{\text{CF}}$ 239.4, C3); δ_{F} (658MHz, DMSO-d_6) -86.9 (1F, t, $^3J_{\text{FF}}$ 27.6, F3/6), -101.0 (1F, t, $^3J_{\text{FF}}$ 27.6, F3/6), -140.0 (1F, t, $^3J_{\text{FF}}$ 27.6, F5); m/z (EI^+) 252 (32%, $[\text{M}]^+$), 104 (61, $[\text{NHCPH}]^+$), 77 (100, $[\text{Ph}]^+$).

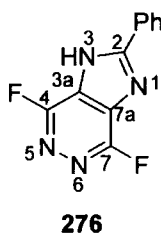
7-Fluoro-N,N-diisopropyl-2-phenyl-1H-imidazo[4,5-d]pyridazin-4-amine 275



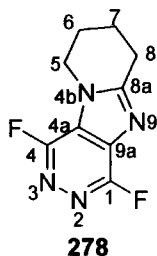
N-(3,5,6-trifluoropyridazin-4-yl)benzamidine (0.10g, 0.396mmol) was dissolved in dry THF (10ml) under argon with stirring at 0°C , and lithium diisopropylamide (0.44ml, 1.8M in hexanes, 0.793mmol) was added dropwise. The mixture was allowed to warm to room temperature before being heated to 80°C for 2 hours. After this period water (10ml) was added slowly, followed by ethyl acetate (20ml) and the layers separated. The aqueous layer was extracted with ethyl acetate (2×20 ml), and the combined organic extracts were dried (MgSO_4), filtered and evaporated *in vacuo* to yield a crude brown product (0.07g, 76%). Purification was not attempted due to a lack of material and the complex product mixture obtained but the major product was identified as *7-fluoro-N,N-diisopropyl-2-phenyl-1H-imidazo[4,5-d]pyridazin-4-amine 275*; δ_{H} (300MHz, CDCl_3) 5.70 (1H, s, NH), 7.54 – 7.10 (4H, m, ArH), 8.30 (1H, m, ArH); δ_{F} (188MHz, CDCl_3) -100.0 (1F, s); m/z (EI^+) 314 (100%, $[\text{M}]^+$), 210 (8), 131 (25), 117 (22), 92 (20), 91 (100).

N-(7-Fluoro-2-phenyl-1*H*-imidazo[4,5-*d*]pyridazin-4-yl)benzamidinium 277

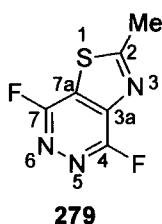
Tetrafluoropyridazine (0.50g, 3.29mmol) was dissolved in acetonitrile (5ml) in a 2-5ml microwave vial. Benzamidinium hydrochloride (1.29g, 8.22mmol) was added and the vial sealed. The mixture was heated under microwave irradiation at 150°C for 30 minutes, after which ^{19}F NMR showed the formation of a complex product mixture. Purification by column chromatography was not possible, however the mixture was shown to contain *N*-(7-fluoro-2-phenyl-1*H*-imidazo[4,5-*d*]pyridazin-4-yl)benzamidinium 277; δ_{F} (188MHz, CDCl_3) -80.3 (1F, s); m/z (EI) 332 (8%, $[\text{M}]^+$), 295 (37), 269 (58), 267 (100), 127 (59), 125 (81).

N-(3,5,6-trifluoro-2-phenyl-1*H*-imidazo[4,5-*d*]pyridazin-4-yl)benzamidinium 276

N-(3,5,6-trifluoropyridazin-4-yl)benzamidinium (0.25g, 0.99mmol) was dissolved in dry acetonitrile (2.5ml) in a 2-5ml microwave vial, and diisopropylethylamine (0.17ml, 0.99mmol) was added). The vial was then capped and irradiated at 150°C for 60 minutes. After this period water (25ml) was added, followed by dichloromethane (25ml). The layers were then separated, and the aqueous layer extracted with 2 further portions of dichloromethane (2 × 25ml). The combined organic extracts were dried (MgSO_4), filtered and evaporated to yield a crude yellow material. This was then recrystallised from toluene to yield 4,7-difluoro-2-phenyl-1*H*-imidazo[4,5-*d*]pyridazine 276 (0.19g, 62%) as yellow solid; mp 220°C (decomp.) (Found $[\text{MH}]^+$ 233.06326. $\text{C}_{11}\text{H}_6\text{F}_2\text{N}_4$ requires $[\text{MH}]^+$ 233.06333); δ_{H} (500MHz, CDCl_3) 7.64 (3H, m, ArH), 8.21 (2H, m, ArH); δ_{C} (100MHz, $\text{DMSO}-d_6$) 127.5 (s, ArC), 129.0 (s, ArC), 129.7 (s, ArC), 131.0 (s, ArC), 154.8 (d, $^2J_{\text{FF}}$ 19.8, C3a,7a), 155.9 (dd, $^1J_{\text{CF}}$ 243.4, $^4J_{\text{CF}}$ 8.7, C4,7), 159.0 (s, C2); δ_{F} (376MHz, CDCl_3) -89.3 (1F, s); m/z (ES^+) 233 ($[\text{M}+\text{H}]^+$, 100%).

1,4-Difluoro-5,6,7,8-tetrahydro-2,3,4b,9-tetraaza-fluorene 278

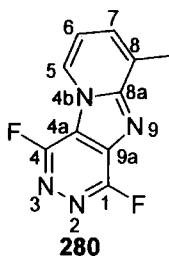
Tetrafluoropyridazine (0.50g, 3.28mmol) was mixed with 2-iminopiperidine (0.98g, 7.22mmol) and sodium hydrogencarbonate (1.10g, 13.1mmol) in acetonitrile (100ml) under argon. The mixture was stirred at room temperature for 60 hours, after which the solvent was evaporated, and the crude mixture dissolved in ethyl acetate (25ml) and water (50ml). The aqueous layer was separated and acidified with HCl (10%), then extracted with ethyl acetate (2 × 25ml) and dichloromethane (3 × 25ml). The combined organic extracts were dried (MgSO₄), filtered and the solvent evaporated to yield a crude brown product (0.64g), which was purified by flash column chromatography with elutant ethyl acetate / dichloromethane (2:1), to yield *1,4-difluoro-5,6,7,8-tetrahydro-2,3,4b,9-tetraaza-fluorene 278* (0.57g, 82%) as a yellow solid; mp 152 – 154°C (Found C, 51.0; H, 3.9; N, 26.7. C₉H₈N₄F₂ requires C, 51.4; H, 3.8; N, 26.4%); δ_{H} (500MHz, CDCl₃) 2.09 (2H, m), 2.19 (2H, m), 3.22 (2H, t, $^3J_{\text{HH}}$ 7.0, C8(H)), 4.40 (2H, t, $^3J_{\text{HH}}$ 5.8, C5(H)); δ_{C} (125MHz, CDCl₃), 19.7 (s), 22.2 (s), 25.6 (s), 45.9 (s, C5), 125.1 (dd, $^2J_{\text{CF}}$ 28.0, $^3J_{\text{CF}}$ 11.7, C4a/9a), 133.5 (dd, $^2J_{\text{CF}}$ 32.9, $^3J_{\text{CF}}$ 6.5, C4a/9a), 153.4 (d, $^1J_{\text{CF}}$ 237.6, C1/4), 157.6 (d, $^1J_{\text{CF}}$ 244.4, C1/4), 157.7 (s, C8a); δ_{F} (376MHz, CDCl₃) -92.6 (1F, d, $^5J_{\text{FF}}$ 32.9), -94.6 (1F, d, $^5J_{\text{FF}}$ 32.9); m/z (EI⁺) 210 (100%, [M]⁺), 209 (36, [M-H]⁺), 182 (32), 181 (14).

4,7-Difluoro-2-methylthiazolo[4,5-d]pyridazine 279

Tetrafluoropyridazine (1.00g, 6.58mmol) was mixed with thioacetamide (0.54g, 7.23mmol) and sodium hydrogen carbonate (2.21g, 26.3mmol) in acetonitrile (50ml) under argon. The mixture was stirred at reflux for 16 hours, after which the solvent was

evaporated, and the crude mixture dissolved in ethyl acetate (25ml) and water (25ml). The aqueous layer was separated and acidified with HCl (10%), then extracted with ethyl acetate (2 × 25ml) and dichloromethane (3 × 25ml). The combined organic extracts were dried (MgSO₄), filtered and the solvent evaporated to yield a crude brown product, which was purified by elution through silica gel with ethyl acetate, followed by recrystallisation from acetonitrile, to yield *4,7-difluoro-2-methylthiazolo[4,5-d]pyridazine* **279** (0.76g, 62%); as yellow solid, mp > 250°C (Found C, 38.9; H, 1.7; N, 22.7. C₆H₃N₃F₂S requires C, 38.5; H, 1.6; N, 22.5%); δ_H (700MHz, DMSO-d₆) 3.00 (3H, s, CH₃); δ_C (175MHz, CDCl₃) 20.7 (s, CH₃), 129.4 (dd, ²J_{CF} 38.8, ³J_{CF} 16.8, C3a/7a), 161.0 (dd, ¹J_{CF} 243.0, ⁴J_{CF} 6.0, C4/7), 178.9 (s, C2); δ_F (658MHz, DMSO-d₆) -81.4 (2F, s); *m/z* (EI⁺) 187 (30%, [M]⁺), 117 (24), 87 (100), 70 (92), 31 (97).

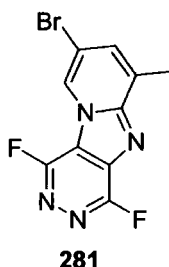
1,4-Difluoro-8-methyl-2,3,4b,9-tetraaza-fluorene **280**



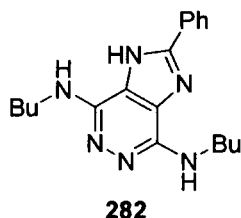
Tetrafluoropyridazine (0.50g, 3.28mmol) was mixed with 2-amino-3-picoline (0.83ml, 8.22mmol) and acetonitrile (1ml) in a 2-5ml microwave vial, which was capped and sealed. This was irradiated at 150°C for 10 minutes, after which the solvent was evaporated and the residue dissolved in dichloromethane (20ml), and washed with water (20ml). The aqueous layer was then extracted with dichloromethane (3 × 20ml) and the combined organic extracts were dried (MgSO₄), filtered, and evaporated *in vacuo* to yield a crude brown product. This was purified by filtration through a small plug of silica gel with dichloromethane as elutant, yielding *1,4-difluoro-8-methyl-2,3,4b,9-tetraaza-fluorene* **280** (0.42g, 58%) as a white solid; mp 213 – 215°C (Found [MH]⁺ 221.06339. C₁₀H₆N₄F₂ requires [MH]⁺ 221.06333); ν_{max} / cm⁻¹ 976, 1024, 1102, 1165, 1228, 1256, 1281, 1309, 1379, 1433, 1580; δ_H (500MHz, CDCl₃) 2.79 (3H, s, CH₃), 7.21 (1H, t, ³J_{HH} 7.2, C6(H)), 7.59 (1H, d, ³J_{HH} 7.2, C7(H)), 8.63 (1H, d, ³J_{HH} 7.2, C5(H)); δ_C (125MHz, CDCl₃) 17.7 (s, CH₃), 115.6 (s, ArC), 119.0 (dd, ²J_{CF} 26.9, ³J_{CF} 11.6, C4a/9a), 125.6 (d, ⁴J_{CF} 4.9, C5), 130.1 (s, ArC), 131.8 (s, ArC), 135.3 (dd, ²J_{CF} 35.1, ³J_{CF} 6.2, C4a/9a), 151.9 (m, C8a), 154.0 (dd,

$^1J_{CF}$ 238.6, $^4J_{CF}$ 2.4, C1/4), 158.2 (dd, $^1J_{CF}$ 246.9, $^4J_{CF}$ 3.5, C1/4); δ_F (376MHz, $CDCl_3$) -89.7 (1F, d, $^5J_{FF}$ 34.6), -91.6 (1F, d, $^5J_{FF}$ 34.6); m/z (EI^+) 220 (100%, $[M]^+$); λ_{max} (fluorescence) 360nm.

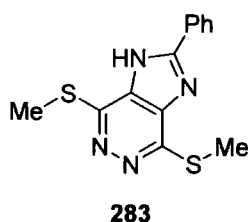
6-Bromo-1,4-difluoro-8-methyl-2,3,4b,9-tetraaza-fluorene 281



Tetrafluoropyridazine (0.50g, 3.28mmol) was mixed with 2-amino-5-bromo-3-methylpyridine (1.68g, 8.20mmol) and acetonitrile (10ml) in a 10-20ml microwave vial, which was capped and sealed. This was irradiated at 120°C for 60 minutes, followed by irradiation at 150°C for a further 60 minutes to achieve complete conversion. The solvent was evaporated and the residue dissolved in dichloromethane (20ml), and washed with water (20ml). The aqueous layer was then extracted with dichloromethane (3 × 20ml) and the combined organic extracts were dried ($MgSO_4$), filtered, and evaporated *in vacuo* to yield a crude brown product. This was purified by filtration through a small plug of silica gel with dichloromethane as elutant, then recrystallised from ethyl acetate and hexane (1:2) to yield **6-Bromo-1,4-difluoro-8-methyl-2,3,4b,9-tetraaza-fluorene 281** (0.36g, 40%) as a cream solid; mp 215 – 217°C (Found C, 40.2; H, 2.0; N, 18.5. $C_{10}H_6N_4F_2$ requires C, 40.2; H, 1.7; N, 18.7%); ν_{max} / cm^{-1} 996, 1028, 1106, 1159, 1247, 1279, 1310, 1326, 1413, 1433, 1470, 1558; δ_H (400MHz, $CDCl_3$) 2.78 (3H, s, CH_3), 7.66 (1H, s, C5/7(H)), 8.73 (1H, s, C5/7(H)); δ_C (100MHz, $CDCl_3$) 17.5 (s, Me), 110.2 (s, C6/7/8), 118.6 (dd, $^3J_{CF}$ 26.9, $^2J_{CF}$ 11.9, C4a/9a), 125.4 (d, $^4J_{CF}$ 4.6, C5), 131.0 (s, C6/7/8), 135.1 (dd, $^2J_{CF}$ 36.4, $^3J_{CF}$ 6.9, C4a/9a), 135.3 (s, C6/7/8), 150.1 (d, $^4J_{CF}$ 2.0, C8a), 153.6 (dd, $^1J_{CF}$ 236.8, $^4J_{CF}$ 2.8, C1/4), 158.2 (dd, $^1J_{CF}$ 246.8, $^4J_{CF}$ 3.4, C1/4); δ_F (376MHz, $CDCl_3$) -89.0 (1F, d, $^5J_{FF}$ 34.8), -90.9 (1F, d, $^5J_{FF}$ 34.8); m/z (EI^+) 300 (100%, $[M^+, ^{81}Br]$), 298 (93, $[M^+, ^{79}Br]$), 219 (62, $[M-Br]^+$), 154 (26, $[C_5F_2N_4]^+$), 102 (40, $[C_3F_2N_2]^+$), 90 (30, $[C_2F_2N_2]^+$), 77 (44), 63 (57), 51 (60), 39 (34).

N4,N7-Dibutyl-2-phenyl-1H-imidazo[4,5-d]pyridazine-4,7-diamine 282

4,7-Difluoro-2-phenyl-1*H*-imidazo[4,5-*d*]pyridazine (0.10g, 0.43mmol) was dissolved in acetonitrile (1ml) in a 0.5-2ml microwave vial and *n*-butylamine (0.085ml, 0.86mmol) was added and the vial sealed. The mixture was heated under microwave irradiation at 150°C for 20 minutes before dichloromethane (10ml) and water (10ml) were added and the layers separated. The aqueous layer was then washed with further portions of dichloromethane (3 × 10ml) and the organic extracts combined, dried (MgSO₄), filtered and evaporated to yield a crude yellow material. This was purified by elution through silica gel using ethyl acetate as elutant to yield *N4,N7-dibutyl-2-phenyl-1H-imidazo[4,5-d]pyridazine-4,7-diamine 282* (0.051g, 35%) as yellow crystals; mp 173 – 175°C; δ_{H} (500MHz, CDCl₃) 0.87 (6H, m, NHCH₂CH₂CH₂CH₃), 1.33 (4H, sextet, ³J_{HH} 7.4, NHCH₂CH₂CH₂CH₃), 1.61 (4H, pent, ³J_{HH} 7.4, NHCH₂CH₂CH₂CH₃), 3.36 (4H, t, ³J_{HH} 7.4, NHCH₂CH₂CH₂CH₃), 7.39 (3H, m, C2'/4'(H)), 8.19 (1H, m, C3'(H)); δ_{C} (125MHz, CDCl₃) 13.9 (s, NHCH₂CH₂CH₂CH₂), 20.3 (s, NHCH₂CH₂CH₂CH₂), 31.3 (s, NHCH₂CH₂CH₂CH₂), 41.7 (s, NHCH₂CH₂CH₂CH₂), 116.2 (s), 118.9 (s), 127.3 (s), 129.0 (s), 129.7 (s), 132.7 (s), 147.1 (s); *m/z* (ES⁺) 339 (100%, [M+H]⁺).

4,7-Bis(methylthio)-2-phenyl-1H-imidazo[4,5-d]pyridazine 283

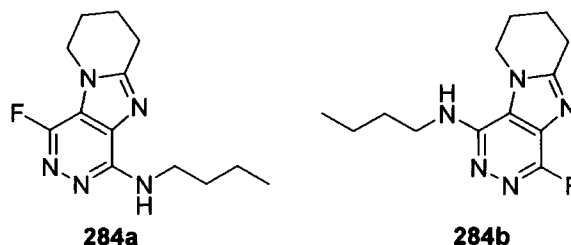
4,7-Difluoro-2-phenyl-1*H*-imidazo[4,5-*d*]pyridazine (0.10g, 0.43mmol) was dissolved in acetonitrile (1ml) in a 0.5-2ml microwave vial and *n*-butylamine (0.060g, 0.86mmol) was added and the vial sealed. The mixture was heated under microwave irradiation at 150°C for 20 minutes before dichloromethane (10ml) and water (10ml) were added and the layers separated. The aqueous layer was then washed with further portions

of dichloromethane ($3 \times 10\text{ml}$) and the organic extracts combined, dried (MgSO_4), filtered and evaporated to yield a crude yellow material. This could not be fully purified by flash column chromatography using ethyl acetate and hexane (1:2) as elutant. The major product was *4,7-bis(methylthio)-2-phenyl-1H-imidazo[4,5-d]pyridazine* **283** (0.040g, 32%); δ_{H} (400MHz, CDCl_3) 2.21 (3H, s, CH_3), 7.06 – 7.45 (5H, m, ArH); m/z (ES^+) 289 (100%, $[\text{M}+\text{H}]^+$).

Attempted bromination of 4,7-difluoro-2-phenyl-1H-imidazo[4,5-d]pyridazine

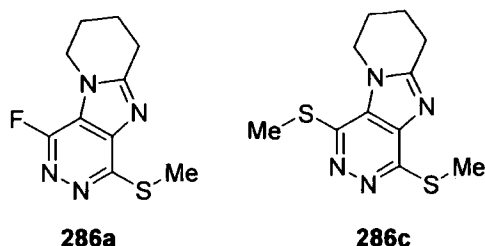
4,7-Difluoro-2-phenyl-1H-imidazo[4,5-d]pyridazine (0.10g, 0.431mmol) was dissolved in dry dichloromethane (20ml) and iron filings (0.026g, 0.473mmol) and bromine (0.11ml, 2.15mmol) were added. The mixture was heated to reflux under argon for 8 hours, after which ^{19}F NMR and TLC of the reaction mixture confirmed that the starting material had been returned.

4-Fluoro-1-butylamino-5,6,7,8-tetrahydro-2,3,4b,9-tetraaza-fluorene **284a** and *1-fluoro-4-butylamino-5,6,7,8-tetrahydro-2,3,4b,9-tetraaza-fluorene* **284b**



1,4-Difluoro-5,6,7,8-tetrahydro-2,3,4b,9-tetraaza-fluorene (0.10g, 0.48mmol) was dissolved in acetonitrile (1ml) in a 0.5-2ml microwave vial and *n*-butylamine (0.094ml, 0.95mmol) was added. The vial was sealed and the mixture was heated under microwave irradiation at 150°C for 20 minutes. After this period dichloromethane (10ml) and water (10ml) were added and the layers separated. The aqueous layer was then washed with further portions of dichloromethane ($3 \times 10\text{ml}$) and the organic extracts combined, dried (MgSO_4), filtered and evaporated to yield a crude yellow material. Purification by flash column chromatography using ethyl acetate and hexane (2:1) as elutant was attempted, however it proved impossible to separate the regioisomers. The mixture contained *4-fluoro-1-butylamino-5,6,7,8-tetrahydro-2,3,4b,9-tetraaza-fluorene* **284a** as a yellow solid;

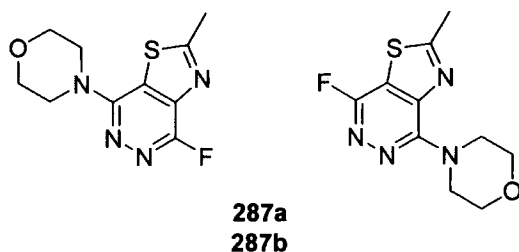
4-Fluoro-1-methylthio-5,6,7,8-tetrahydro-2,3,4b,9-tetraaza-fluorene **286a** and *1,4-bis-(methylthio)-5,6,7,8-tetrahydro-2,3,4b,9-tetraaza-fluorene* **286c**



1,4-Difluoro-5,6,7,8-tetrahydro-2,3,4b,9-tetraaza-fluorene (0.10g, 0.48mmol) was dissolved in acetonitrile (1ml) in a 0.5-2ml microwave vial and sodium thiomethoxide (0.067g, 0.95mmol) was added. The vial was sealed and the mixture was heated under microwave irradiation at 150°C for 20 minutes. After this period dichloromethane (10ml) and water (10ml) were added and the layers separated. The aqueous layer was then washed with further portions of dichloromethane (3 × 10ml) and the organic extracts combined, dried (MgSO₄), filtered and evaporated to yield a crude yellow material. Attempted purification by flash column chromatography using ethyl acetate and hexane (2:1) as elutant failed to separate the two products, which were *4-fluoro-1-methylthio-5,6,7,8-tetrahydro-2,3,4b,9-tetraaza-fluorene* **286a**; δ_H (500MHz, CDCl₃) 2.14 (4H, m), 2.80 (3H, s, CH₃), 3.15 (2H, t, ³J_{HH} 6.9), 4.33 (2H, t, ³J_{HH} 6.5); δ_F (658MHz, CDCl₃) -96.3 (1F, s); m/z (ES⁺) 239 (100%, [M+H]⁺).

Also produced was *1,4-bis-(methylthio)-5,6,7,8-tetrahydro-2,3,4b,9-tetraaza-fluorene* **286c** δ_H (500MHz, CDCl₃) 2.02 (4H, m), 2.77 (3H, s, CH₃), 2.80 (3H, s, CH₃), 3.13 (2H, t, ³J_{HH} 6.7), 4.51 (2H, t, ³J_{HH} 6.3); m/z (ES⁺) 267 (100%, [M+H]⁺).

4-Fluoro-2-methyl-7-morpholinothiazolo[4,5-d]pyridazine and *7-fluoro-2-methyl-4-morpholinothiazolo[4,5-d]pyridazine* (**287a** and **287b**)

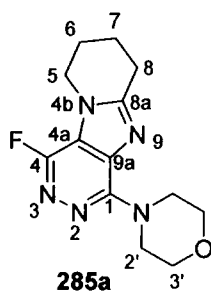


4,7-difluoro-2-methylthiazolo[4,5-d]pyridazine (0.10g, 0.534mmol) was dissolved in dry acetonitrile (1ml) in a 0.5-2ml microwave vial and morpholine (0.051ml,

δ_{H} (400MHz, CDCl_3) 0.93 (3H, t, $^3J_{\text{HH}}$ 7.4, $\text{NHCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 1.44 (2H, sextet, $^3J_{\text{HH}}$ 7.4, $\text{NHCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 1.67 (2H, pent, $^3J_{\text{HH}}$ 7.4, $\text{NHCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 2.10 (4H, m), 3.08 (2H, t, $^3J_{\text{HH}}$ 6.4, C8), 3.62 (2H, q, $^3J_{\text{HH}}$ 7.1, $\text{NHCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 4.30 (2H, t, $^3J_{\text{HH}}$ 6.0, C5), 5.12 (1H, br t, $^3J_{\text{HH}}$ 5.3 $\text{NHCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$); δ_{F} (658MHz, CDCl_3) -102.0 (1F, s); m/z (ES^+) 264 (100%, $[\text{M}+\text{H}]^+$).

The minor product was 1-fluoro-4-butylamino-5,6,7,8-tetrahydro-2,3,4b,9-tetraaza-fluorene **284b** δ_{F} (376MHz, CDCl_3) -101.7 (1F, s); m/z (ES^+) 264 (100%, $[\text{M}+\text{H}]^+$).

4-Fluoro-1-morpholin-4-yl-5,6,7,8-tetrahydro-2,3,4b,9-tetraaza-fluorene **285a**

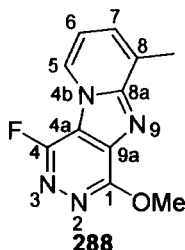


1,4-Difluoro-5,6,7,8-tetrahydro-2,3,4b,9-tetraaza-fluorene (0.10g, 0.48mmol) was dissolved in acetonitrile (1ml) in a 0.5-2ml microwave vial and morpholine (0.083ml, 0.95mmol) was added. The vial was sealed and the mixture was heated under microwave irradiation at 150°C for 20 minutes. After this period dichloromethane (10ml) and water (10ml) were added and the layers separated. The aqueous layer was then washed with further portions of dichloromethane (3 × 10ml) and the organic extracts combined, dried (MgSO_4), filtered and evaporated to yield a crude yellow material. This was purified by flash column chromatography using ethyl acetate and hexane (2:1) as elutant to yield 4-fluoro-1-morpholin-4-yl-5,6,7,8-tetrahydro-2,3,4b,9-tetraaza-fluorene **285a** (0.095g, 72%) as yellow solid; mp 179 – 181°C (Found $[\text{MH}]^+$ 278.14106. $\text{C}_{13}\text{H}_{16}\text{N}_5\text{FO}$ requires $[\text{MH}]^+$ 278.14117); δ_{H} (500MHz, CDCl_3) 2.04 (2H, m), 2.14 (2H, m), 3.09 (2H, t, $^3J_{\text{HH}}$ 6.4, C8(H)), 3.87 (4H, t, $^3J_{\text{HH}}$ 4.8, C2'(H)), 4.03 (4H, t, $^3J_{\text{HH}}$ 4.8, C3'(H)), 4.33 (2H, t, $^3J_{\text{HH}}$ 6.0, C5(H)); δ_{C} (125MHz, CDCl_3), 20.2 (s), 22.6 (s), 25.5 (s), 45.3 (d, $^4J_{\text{CF}}$ 2.7, C5), 47.3 (s, C2'), 67.2 (s, C3'), 125.1 (d, $^2J_{\text{CF}}$ 27.6, C4a), 136.1 (d, $^3J_{\text{CF}}$ 5.8, C9a), 151.5 (d, $^1J_{\text{CF}}$ 231.6, C4), 152.6 (d, $^4J_{\text{CF}}$ 2.1, C1), 153.9 (d, $^4J_{\text{CF}}$ 2.1, C8a); δ_{F} (658MHz, CDCl_3) -101.9 (1F, s); m/z (ES^+) 278 (100%, $[\text{M}+\text{H}]^+$).

0.587mmol) and DIPEA (0.102mol, 0.587mmol) were added. The vial was sealed and the mixture irradiated at 150°C for 20 minutes. After this period the solvent was evaporated and the mixture redissolved in dichloromethane (10ml) and water (10ml). The aqueous layer was separated and washed with further portions of dichloromethane (3 × 10ml). The organic extracts were combined, dried (MgSO₄), filtered and evaporated *in vacuo*. This yielded a mixture of two products, which unfortunately could not be conclusively identified. They were most likely *4-fluoro-2-methyl-7-morpholinothiazolo[4,5-d]pyridazine* and *7-fluoro-2-methyl-4-morpholinothiazolo[4,5-d]pyridazine* (**287a** and **287b**). The major product δ_{H} (400MHz, CDCl₃) 2.86 (3H, s, CH₃), 3.84 (4H, t, ³J_{HH} 4.7, C2'(H)), 3.99 (4H, t, ³J_{HH} 4.7, C3'(H)); δ_{F} (376MHz, CDCl₃) -85.4 (1F, s); *m/z* (ES⁺) 255 (100%, [M+H]⁺).

The minor product δ_{H} (400MHz, CDCl₃) 2.93 (3H, s, CH₃), 3.49 (4H, t, ³J_{HH} 5.1, C2'(H)), 4.12 (4H, t, ³J_{HH} 5.1, C3'(H)); δ_{F} (376MHz, CDCl₃) -84.8 (1F, s); *m/z* (ES⁺) 255 (100%, [M+H]⁺).

4-Fluoro-1-methoxy-8-methyl-2,3,4b,9-tetraaza-fluorene **288**

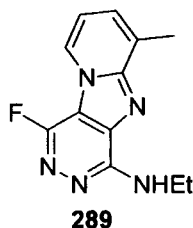


1,4-Difluoro-8-methyl-2,3,4b,9-tetraaza-fluorene (0.50g, 2.27mmol) was mixed with sodium methoxide (0.31g, 5.68mmol) in methanol (3ml) in a 2-5ml microwave vial, which was sealed and irradiated at 120°C for 10 minutes. After this irradiation period water (15ml) was added, followed by dichloromethane (15ml), and the layers separated. The aqueous layer was extracted with dichloromethane (3 × 20ml), and the organic extracts were combined, dried (MgSO₄), filtered and evaporated to yield a crude red brown material (0.48g), containing 2 products in a 3:1 ratio by ¹⁹F NMR. This was purified by flash column chromatography (Hexane : Ethyl Acetate 2:1) to yield *4-Fluoro-1-methoxy-8-methyl-2,3,4b,9-tetraaza-fluorene* **288** (0.21g, 40%) as a white solid; mp 229 – 231°C (Found C, 56.6; H, 3.9; N, 23.9. C₁₁H₉FN₄O requires C, 56.9; H, 3.9; N, 24.1%); ν_{max} / cm⁻¹ 964, 980, 1030, 1102, 1132, 1168, 1236, 1286, 1320, 1372, 1424, 1466, 1579; δ_{H}

(500MHz, CDCl₃) 2.76 (3H, s, C8(CH₃)), 4.38 (3H, s, OCH₃), 7.08 (1H, t, ³J_{HH} 6.8, C6(H)), 7.48 (1H, dt, ³J_{HH} 6.8, ⁴J_{HH} 1.0, C7(H)), 8.80 (1H, d, ³J_{HH} 6.8, C5(H)); δ_C (125MHz, CDCl₃) 17.6 (s, C8(CH₃)), 55.6 (s, OCH₃), 114.3 (s), 120.5 (d, ³J_{CF} 11.4, C9a), 126.0 (s), 129.1 (s), 130.4 (s), 133.1 (d, ²J_{CF} 36.4, C4a), 150.7 (s, C8a), 154.9 (d, ⁴J_{CF} 2.0, C1), 156.8 (d, ¹J_{CF} 247.6, C4); δ_F (376MHz, CDCl₃) -94.5 (1F, s); *m/z* (EI⁺) 232 (58%, [M⁺]), 231 (39, [M-H]⁺), 217 (8, [M-Me]⁺), 183 (100).

The minor product *1-Fluoro-4-methoxy-8-methyl-2,3,4b,9-tetraaza-fluorene* was not isolated pure; δ_F (200MHz, CDCl₃) -95.6 (1F, s); *m/z* (EI⁺) 232 (94%, [M⁺]), 231 (91, [M-H]⁺), 217 (24, [M-Me]⁺), 183 (100).

Ethyl-(4-fluoro-8-methyl-2,3,4b,9-tetraaza-fluoren-1-yl)-amine 289

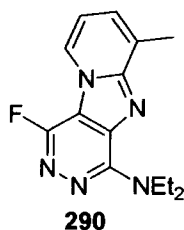


1,4-Difluoro-8-methyl-2,3,4b,9-tetraaza-fluorene (0.50g, 2.27mmol) was mixed with ethylamine (2.83ml, 2.0M in THF, 5.68mmol) in a 2-5ml microwave vial, which was sealed and irradiated at 120°C for 10 minutes. After this irradiation period water (15ml) was added, followed by dichloromethane (15ml), and the layers separated. The aqueous layer was extracted with dichloromethane (3 × 20ml), and the organic extracts were combined, dried (MgSO₄), filtered and evaporated to yield a crude red brown material (0.45g). This was recrystallised from toluene to yield *Ethyl-(4-fluoro-8-methyl-2,3,4b,9-tetraaza-fluoren-1-yl)-amine 289* as yellow solid (0.36g, 65%); mp 127 – 129°C (Found [MH]⁺ 246.11492. C₁₂H₁₂FN₅ requires [MH]⁺ 246.11495); ν_{max} / cm⁻¹ 1056, 1081, 1108, 1160, 1231, 1320, 1340, 1401, 1435, 1480, 1583, 1616, 3351 (br, NH); δ_H (500MHz, CDCl₃) 1.40 (3H, t, ³J_{HH} 6.6, NHCH₂CH₃), 2.71 (3H, s, ring CH₃), 3.77 (4H, quin, ³J_{HH} 6.6, NHCH₂CH₃), 5.53 (1H, br t, ³J_{HH} 6.6, NHet), 7.03 (1H, t, ³J_{HH} 6.7, C6), 7.40 (1H, dt, ³J_{HH} 6.7, ⁴J_{HH} 0.9), 8.51 (1H, d, ³J_{HH} 6.7, C5); δ_C (125MHz, CDCl₃) 14.9 (s, NHCH₂CH₃), 17.5 (s, C8(CH₃)), 36.5 (s, NHCH₂CH₃), 114.2 (s), 114.5 (d, ²J_{CF} 29.5, C4a), 125.5 (d, J_{CF} 4.2, C9a), 128.9 (s), 129.5 (s), 136.3 (d, ⁴J_{CF} 4.5, C5), 149.6 (d, ⁴J_{CF} 2.7, C8a), 150.2 (d, ¹J_{CF}

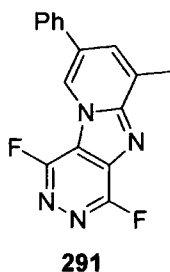
230.6, C4), 153.1 (d, $^4J_{CF}$ 2.0, C1); δ_F (376MHz, $CDCl_3$) -99.4 (1F, s); m/z (EI^+) 245 (17%, $[M]^+$), 230 (29, $[M-Me]^+$), 183 (67), 92 (58), 65 (69), 29 (100, $[Et]^+$).

Minor isomer was not isolated, most probably *Ethyl-(1-fluoro-8-methyl-2,3,4b,9-tetraaza-fluoren-4-yl)-amine*; δ_F (200MHz, $CDCl_3$) -98.5 (1F, s); m/z (EI^+) 245 (74, $[M]^+$), 230 (100, $[M-Me]^+$), 183 (95).

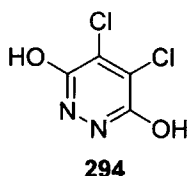
Diethyl-(4-fluoro-8-methyl-2,3,4b,9-tetraaza-fluoren-1-yl)-amine 290



1,4-Difluoro-8-methyl-2,3,4b,9-tetraaza-fluorene (0.30g, 1.36mmol) was mixed with diethylamine (0.35ml, 3.41mmol) in acetonitrile (3ml) in a 2-5ml microwave vial, which was sealed and irradiated at 150°C for 12 minutes. After this irradiation period water (15ml) was added, followed by dichloromethane (15ml), and the layers separated. The aqueous layer was extracted with dichloromethane (3 × 20ml), and the organic extracts were combined, dried ($MgSO_4$), filtered and evaporated to yield a crude red brown material (0.34g). This was recrystallised from hexane / dichloromethane (4:1) to yield *Diethyl-(4-fluoro-8-methyl-2,3,4b,9-tetraaza-fluoren-1-yl)-amine 290* (0.26g, 70%) as yellow crystals; mp 111 – 113°C (Found C, 61.7; H, 5.9; N, 25.4. $C_{10}H_6N_4F_2$ requires C, 61.5; H, 5.9; N, 25.6%); ν_{max} 1000, 1030, 1074, 1098, 1217, 1237, 1295, 1352, 1429, 1485, 1575, 1638, 2973 (CH); δ_H (400MHz, $CDCl_3$) 1.31 (6H, t, $^3J_{HH}$ 7.1, NCH_2CH_3), 2.66 (3H, s, C8(CH_3)), 4.09 (4H, q, $^3J_{HH}$ 7.1, NCH_2CH_3), 6.95 (1H, t, $^3J_{HH}$ 7.0, C6(H)), 7.31 (1H, d, $^3J_{HH}$ 7.0, C7(H)), 8.46 (1H, d, $^3J_{HH}$ 7.0, C5(H)); δ_C (100MHz, $CDCl_3$) 13.8 (s, NCH_2CH_3), 17.3 (s, C8(CH_3)), 44.0 (s, NCH_2CH_3), 113.9 (s), 125.1 (d, $^3J_{CF}$ 5.3, C9a), 128.7 (s), 129.2 (s), 136.6 (d, $^4J_{CF}$ 4.6, C5), 148.3 (d, $^4J_{CF}$ 2.2, C8a), 150.5 (d, $^1J_{CF}$ 228.4, C4), 153.3 (d, $^4J_{CF}$ 1.9, C1); δ_F (376MHz, $CDCl_3$) -102.7 (1F, s); m/z (EI^+) 273 (24%, $[M]^+$), 244 (100, $[M-Et]^+$), 230 (74, $[M-Et-Me]^+$), 201 (12, $[M-NEt_2]^+$), 183 (56), 92 (36); Crystals suitable for X-ray diffraction grown from slow evaporation of ethyl acetate and hexane (1:4).

6-Phenyl-1,4-difluoro-8-methyl-2,3,4b,9-tetraaza-fluorene 291

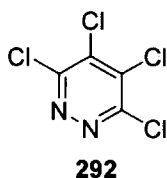
6-Bromo-1,4-difluoro-8-methyl-2,3,4b,9-tetraaza-fluorene (0.10g, 0.334mmol) was mixed with phenyl boronic acid (0.045g, 0.367mmol), caesium carbonate (0.22g, 0.669mmol) and triphenylphosphine (0.013g, 0.0502mmol) and palladium (II) acetate (0.0038g, 0.0167mmol) and dissolved in degassed toluene and water (10:1) (11ml). The mixture was heated to 90°C under argon for 16 hours before being allowed to cool. Dichloromethane (10ml) and water (10ml) were added and the layers separated. The aqueous layer was extracted with further portions of dichloromethane (3 × 10ml), before the organic extracts were dried (MgSO₄), filtered and evaporated *in vacuo* to yield a crude brown material. This was purified by flash column chromatography (elutant ethyl acetate : hexane, 1:2) to yield **6-Phenyl-1,4-difluoro-8-methyl-2,3,4b,9-tetraaza-fluorene 291** (0.040g, 41%) as a white solid; mp 197 – 198°C (Found [MH]⁺ 297.09460. C₁₆H₁₀N₄F₂ requires [MH]⁺ 297.09463); δ_H (500MHz, CDCl₃) 2.86 (3H, s, C8(CH₃)), 7.50 (1H, t, ³J_{HH} 7.9, C4'(H)), 7.55 (2H, t, ³J_{HH} 7.9, C3'(H)), 7.63 (2H, d, ³J_{HH} 7.9, C2'(H)), 7.84 (1H, s, C7(H)), 8.73 (1H, s, C5(H)); δ_F (376MHz, CDCl₃) -89.1 (1F, d, ⁵J_{FF} 34.4), -91.0 (1F, d, ⁵J_{FF} 34.4); *m/z* (ES⁺) 297 (100%, [M+H]⁺).

7.5 Experimental to Chapter 5**4,5-Dichloropyridazine-3,6-diol 294**

A solution of hydrazine hydrate (31.1ml, 0.63mol) was made up in water (400ml) and conc. HCl (120ml). Dichloromaleic anhydride (100g, 0.60mol) was added with stirring under an argon atmosphere. The suspension was stirred at room temperature for 1 hour,

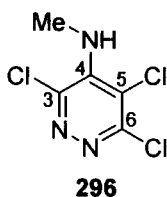
followed by reflux for 2 hours. A crust formed on the surface of the mixture, which was broken up by the addition of a little water. The mixture was allowed to cool and was then filtered to obtain 4,5-dichloropyridazine-3,6-diol¹²¹ **294** (98.85g, 91%, as cream solid), which was dried under vacuum without any further purification and used in the synthesis of tetrachloropyridazine; δ_{H} (400MHz, CDCl_3) 1.54 (2H, br s, OH); m/z (EI) 184 (12%, $[\text{M}]^+$, ($2 \times {}^{37}\text{Cl}$)), 182 (59, $[\text{M}]^+$, ($1 \times {}^{37}\text{Cl}$, $1 \times {}^{35}\text{Cl}$)), 180 (100, $[\text{M}]^+$, ($2 \times {}^{35}\text{Cl}$)).

Tetrachloropyridazine **292**



4,5-dichloropyridazine-3,6-diol (98g, 0.54mol) was added to phosphorus oxychloride and the mixture stirred and refluxed under argon for 7 hours. This was then allowed to cool overnight before being poured slowly onto crushed ice (~2l). This addition was very exothermic and also had an initiation period, so extreme care was necessary. The solid product was then filtered off and dissolved in diethyl ether. Water (100ml) was added and the mixture was separated, dried (MgSO_4), filtered and the solvent evaporated under vacuum to yield a crude cream product (103.09g). This was then recrystallised from methanol to yield tetrachloropyridazine **292** (99.03g, 84%) as white crystals; mp 87 – 89°C (Found C, 22.2; N, 12.8. $\text{C}_4\text{N}_2\text{Cl}_4$ requires C, 22.0; N, 12.9%); δ_{C} (CDCl_3 , 500MHz) 137.5 (s, C4/5), 154.6 (s, C3/6); m/z (EI) 222 (7%, $[\text{M}]^+$ ($3 \times {}^{37}\text{Cl}$, $1 \times {}^{35}\text{Cl}$)), 220 (32, $[\text{M}]^+$ ($2 \times {}^{37}\text{Cl}$, $2 \times {}^{35}\text{Cl}$)), 218 (60, $[\text{M}]^+$ ($1 \times {}^{37}\text{Cl}$, $3 \times {}^{35}\text{Cl}$)), 216 (47, $[\text{M}]^+$ ($4 \times {}^{35}\text{Cl}$)).

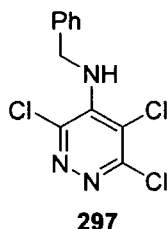
3,5,6-Trichloro-N-methylpyridazin-4-amine **296**



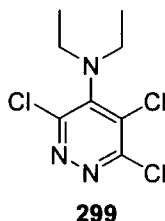
Tetrachloropyridazine (1.00g, 4.59mmol) was dissolved in acetonitrile (25ml) under argon with stirring. Methylamine (2.0M in EtOH) (4.6ml, 9.18mmol) was added and the mixture stirred at room temperature for 25 hours. This period was followed by the slow

addition of water (20ml) and acidification of the solution with 10% HCl, followed by extraction with ethyl acetate (3 × 20ml). The combined organic extracts were dried (MgSO₄), filtered and evaporated under vacuum to yield a crude yellow product (0.62g). This was then recrystallised from hexane / ethyl acetate (2:3) to yield *3,5,6-trichloro-N-methylpyridazin-4-amine* **296** (0.42g, 43%) as a cream / yellow solid; mp 113 – 114°C (Found C, 28.6; H, 1.9; N, 19.5. C₅H₄Cl₃N₃ requires C, 28.3; H, 1.9; N, 19.8%); ν_{\max} / cm⁻¹ 918, 1061, 1083, 1146, 1246, 1346, 1428, 1562, 3333 (br, NH); δ_{H} (CDCl₃, 400MHz) 3.41 (3H, d, ³J_{HH} 5.5, CH₃), 5.26 (1H, br s, NH); δ_{C} (CDCl₃, 100MHz) 33.2 (s, CH₃), 115.8 (s), 142.1 (s), 143.6 (s), 154.8 (s); *m/z* (EI) 215 (4%, [M]⁺ (2 × ³⁷Cl, 1 × ³⁵Cl)), 213 (15, [M]⁺, (1 × ³⁷Cl, 2 × ³⁵Cl)), 211 (18, [M]⁺, (3 × ³⁵Cl)), 187 (4, [M-NHMe]⁺, (2 × ³⁷Cl, 1 × ³⁵Cl)), 185 (15, [M-NHMe]⁺ (1 × ³⁷Cl, 2 × ³⁵Cl)), 183 (16, [M-NHMe]⁺ (3 × ³⁵Cl)).

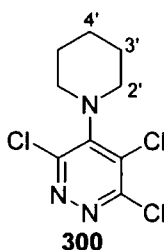
N-Benzyl-3,5,6-trichloropyridazin-4-amine **297**



Tetrachloropyridazine (1.00g, 4.59mmol) was dissolved in acetonitrile (25ml) under argon with stirring. Benzylamine (1.0ml, 9.18mmol) was added and the mixture stirred at room temperature for 16 hours. Water (20ml) was added and the solution acidified with 10% HCl, followed by extraction with ethyl acetate (3 × 20ml). The combined organic extracts were dried (MgSO₄), filtered and evaporated under vacuum to yield a crude yellow product (0.86g). This was then recrystallised from hexane / ethyl acetate (2:1) to yield *N*-benzyl-3,5,6-trichloropyridazin-4-amine **297** (0.71g, 54%) as yellow crystals; mp 75 – 77°C (Found C, 46.0; H, 2.9; N, 14.5. C₁₁H₈N₃Cl₃ requires C, 45.8; H, 2.8; N, 14.6%); ν_{\max} / cm⁻¹ 1088, 1220, 1270, 1338, 1440, 1560, 3317 (br, NH); δ_{H} (CDCl₃, 500MHz) 4.95 (2H, d, ³J_{HH} 5.9, NHCH₂Ph), 5.42 (1H, br s, NHCH₂Ph), 7.29 – 7.40 (5H, m, ArH); δ_{C} (CDCl₃, 125MHz) 49.6 (s, NHCH₂Ph), 116.8 (s), 127.3 (s, PhCH), 128.2 (s, PhCH), 129.1 (s, PhCH), 137.2 (s), 141.4 (s), 144.1 (s), 154.8 (s); *m/z* (EI) 291 (3%, M⁺ (2 × ³⁷Cl, 2 × ³⁵Cl)), 289 (12, [M]⁺ (1 × ³⁷Cl, 3 × ³⁵Cl)), 287 (11, [M]⁺ (4 × ³⁵Cl)), 91 (100, [CH₂Ph]⁺), 77 (11,

3,5,6-Trichloro-*N,N*-diethylpyridazin-4-amine 299

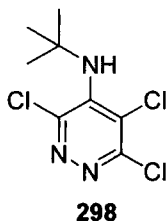
Tetrachloropyridazine (1.00g, 4.59mmol) was dissolved in acetonitrile (25ml) under argon with stirring. Diethylamine (0.95ml, 9.18mmol) was added and the mixture heated to reflux for 16 hours. Water (20ml) was added and the solution acidified with 10% HCl, followed by extraction with ethyl acetate (3 × 20ml). The combined organic extracts were dried (MgSO₄), filtered and evaporated under vacuum to yield a crude red-brown product (1.04g). This was then recrystallised from hexane (10ml) to yield **3,5,6-trichloro-*N,N*-diethylpyridazin-4-amine 299** (0.57g, 49%) as a yellow solid; mp 52 – 54°C (Found C, 37.7; H, 4.0; N, 16.4; C₈H₁₀N₃Cl₃ requires C, 37.8; H, 4.0; N, 16.5%); ν_{\max} / cm⁻¹ 956, 1017, 1078, 1114, 1178, 1234, 1281, 1299, 1319, 1380, 1420, 1469, 1508, 1670, 2936 (CH), 2975 (CH); δ_{H} (CDCl₃, 500MHz) 1.09 (3H, t, ³J_{HH} 7.1, NHCH₂CH₃), 3.37 (2H, q, ³J_{HH} 7.1, NHCH₂CH₃); δ_{C} (CDCl₃, 125MHz) 13.9 (s, NHCH₂CH₃), 45.9 (s, NHCH₂CH₃), 133.2 (s), 146.4 (s), 155.1 (s), 155.4 (s); *m/z* (EI) 257 (3%, [M]⁺ (2 × ³⁷Cl, 1 × ³⁵Cl)), 255 (9, [M]⁺ (1 × ³⁷Cl, 2 × ³⁵Cl)), 253 (12, [M]⁺ (3 × ³⁵Cl)), 242 (22, [M-CH₃]⁺ (2 × ³⁷Cl, 1 × ³⁵Cl)), 240 (63, [M-CH₃]⁺ (1 × ³⁷Cl, 2 × ³⁵Cl)), 238 (60, [M-CH₃]⁺ (3 × ³⁵Cl)), 214 (15, [M-CH₂CH₃]⁺ (2 × ³⁷Cl, 1 × ³⁵Cl)), 212 (45, [M-CH₂CH₃]⁺ (1 × ³⁷Cl, 2 × ³⁵Cl)), 210 (48, [M-CH₂CH₃]⁺ (3 × ³⁵Cl)), 29 (100, [CH₂CH₃]⁺). Crystals suitable for X-ray diffraction were obtained by recrystallisation from hexane.

3,4,6-Trichloro-5-piperidine-1-yl-pyridazine 300

Tetrachloropyridazine (2.00g, 9.17mmol) and piperidine (1.8ml, 18.31mmol) were dissolved in acetonitrile (50ml) and stirred under argon at room temperature for 4 hours. After TLC indicated complete conversion of starting material, water (20ml) was added, and

[Ph]⁺), 65 (63). Crystals suitable for X-ray diffraction were obtained from slow evaporation of ethyl acetate.

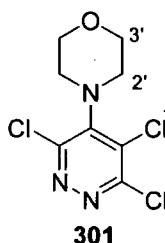
N-tert-Butyl-3,5,6-trichloropyridazin-4-amine **298**



Tetrachloropyridazine (1.00g, 4.59mmol) was dissolved in acetonitrile (25ml) under argon with stirring. *t*-Butylamine (0.96ml, 9.18mmol) was added and the mixture stirred at room temperature for 16 hours, followed by heating to reflux for a further 8 hours. The reaction was quenched by the slow addition of water (20ml), and the solution was acidified with 10% HCl, followed by extraction with ethyl acetate (3 × 20ml). The combined organic extracts were dried (MgSO₄), filtered and evaporated under vacuum to yield a crude yellow product (0.67g). This was then recrystallised from hexane / ethyl acetate (2:3) to yield *N*-tert-butyl-3,5,6-trichloropyridazin-4-amine **298** (0.52g, 45%); as a yellow-orange solid, mp 64 – 66°C (Found C, 37.9; H, 3.8; N, 16.3. C₈H₁₀Cl₃N₃ requires C, 37.8; H, 4.0; N, 16.5%); ν_{\max} / cm⁻¹ 986, 1078, 1193, 1212, 1249, 1341, 1462, 1531, 1557, 1614, 3391 (br, NH); δ_{H} (CDCl₃, 400MHz) 1.49 (9H, s, (CH₃)₃), 4.82 (1H, br s, NH); δ_{C} (CDCl₃, 125MHz) 31.4 (s, NC(CH₃)₃), 57.2 (s, NC(CH₃)₃), 121.7 (s), 142.9 (s), 148.4 (s), 155.0 (s); *m/z* (EI) 255 (2%, M⁺ (1 × ³⁷Cl, 2 × ³⁵Cl)), 253 (2, M⁺ (3 × ³⁵Cl)), 242 (4, [M-CH₃]⁺ (2 × ³⁷Cl, 1 × ³⁵Cl)), 240 (9, [M-CH₃]⁺ (1 × ³⁷Cl, 2 × ³⁵Cl)), 238 (9, [M-CH₃]⁺ (3 × ³⁵Cl)), 201 (5, [M-^tBu] (2 × ³⁷Cl, 1 × ³⁵Cl)), 199 (13, [M-^tBu] (1 × ³⁷Cl, 2 × ³⁵Cl)), 197 (15, [M-^tBu] (3 × ³⁵Cl)), 57 (100, [^t-Bu]⁺), 41 (70, [C(CH₃)₂]⁺), 29 (27, [C(CH₃)]⁺).

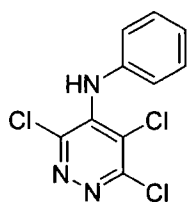
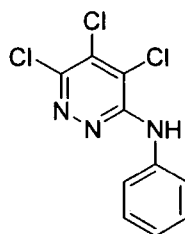
the solution acidified with 10% HCl, and the mixture extracted with ethyl acetate (3 × 20ml). The combined organic extracts were dried (MgSO₄), filtered and evaporated to yield a crude yellow solid (1.48g) which after recrystallisation from ethyl acetate gave *3,4,6-trichloro-5-piperidine-1-yl-pyridazine 300* (0.601g, 25%) as a yellow solid; mp 76 – 78°C (Found C, 40.6; H, 3.8; N, 15.6. C₉H₁₀Cl₃N₃ requires C, 40.6; H, 3.8; N, 15.8%); δ_{H} (500MHz, CDCl₃) 1.73 (6H, m, C3'+4'(H)), 3.33 (4H, t, ³J_{HH} 5.3, C2'(H)); δ_{C} (125MHz, CDCl₃) 23.7 (s, C4'), 26.2 (s, C3'), 51.9 (s, C2') 129.7 (s), 146.8 (s), 152.8 (s) 155.5 (s); *m/z* (EI⁺) 271 (3%, [M]⁺), 270 (5, [M-H]⁺), 269 (18, [M]⁺), 268 (48, [M-H]⁺) 267 (53, [M]⁺), 266 (100, [M-H]⁺), 265 (53, [M]⁺), 264 (100, [M-H]⁺), 55 (35, [C₄H₇]⁺).

4-(3,5,6-Trichloro-pyridazine-4-yl)-morpholine 301



Tetrachloropyridazine (2.00g, 9.17mmol) and morpholine (1.60ml, 18.34mmol) were dissolved in acetonitrile (50ml) under argon with stirring at room temperature. After 24 hours TLC indicated complete conversion of starting material, so water (20ml) was added and the solution acidified with 10% HCl. This was then extracted with ethyl acetate (3 × 20ml) gave a crude yellow product which after recrystallisation from hexane / ethyl acetate (1:1) gave *4-(3,5,6-trichloro-pyridazine-4-yl)-morpholine 301* (1.15g, 47%) as yellow crystals; mp 101 – 103°C (Found C, 35.9; H, 3.0; N, 15.4. C₈H₈N₃OCl₃ requires C, 35.8; H, 3.0; N, 15.7%); δ_{H} (500MHz, CDCl₃) 3.43 (4H, t, ³J_{HH} 4.5, C2'(H)), 3.86 (4H, t, ³J_{HH} 4.5, C3'(H)); δ_{C} (125MHz, CDCl₃) 50.6 (s, C2'), 67.1 (s, C3'), 130.3 (s), 145.5 (s), 152.7 (s), 155.7 (s); *m/z* (EI⁺) 273 (2%, [M]⁺), 272 (2, [M-H]⁺), 271 (15, [M]⁺), 270 (7, [M-H]⁺), 269 (43, [M]⁺), 268 (10, [M-H]⁺), 267 (46, [M]⁺), 266 (6, [M-H]⁺), 234 (30, [M-Cl]⁺), 232 (69, [M-Cl]⁺), 211 (95, [M-C₃H₆O]⁺), 209 (100, [M-C₃H₆O]⁺), 148 (36, [M-C₄H₈NOCl]⁺), 146 (54, [M-C₄H₈NOCl]⁺), 117.9 (32), 85 (23, [C₄H₈NO]⁺), 77 (34).

3,5,6-Trichloro-*N*-phenylpyridazin-4-amine 302a and **4,5,6-trichloro-*N*-phenylpyridazin-3-amine 302b**

**302a****302b**

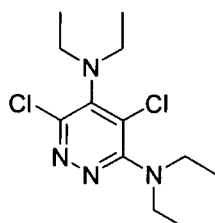
Tetrachloropyridazine (2.00g, 9.17mmol) was dissolved in acetonitrile (50ml) under argon, with stirring. Aniline (0.84ml, 9.17mmol) was added and the mixture stirred, at reflux, for 22 hours. After this period, water (20ml) was added and the solution acidified with 10% HCl. Ethyl acetate (3 × 20ml) was used to extract the product, which was then dried (MgSO₄), filtered and evaporated to yield a black oil. The oil was partially dissolved in DCM. Silica was added to the solution and the solvent was evaporated off. The crude product was purified by flash column chromatography (elutant ethyl acetate / hexane 1:5) to yield pure products.

The major product was identified as *3,5,6-trichloro-N-phenylpyridazin-4-amine 302a* (0.25g, 10%) as a pale orange solid; mp 165 – 167°C (Found C, 43.7; H, 2.2; N, 15.3. C₁₀H₆N₃Cl₃ requires C, 43.8; H, 2.2; N, 15.3%); δ_{H} (400MHz, CDCl₃) 6.75 (1H, br s, NH), 7.02 (2H, d, ³J_{HH} 7.7, C3'(H)), 7.26 (1H, t, ³J_{HH} 7.7, C4'(H)), 7.54 (2H, t, ³J_{HH} 7.7 C2'(H)); δ_{C} (100MHz, CDCl₃) 121.3 (s), 123.6 (s, PhC), 126.5 (s, PhC), 129.3 (s, PhC), 137.8 (s, PhC), 139.1 (s), 146.56 (s), 155.5 (s); *m/z* (EI⁺) 279 (2%, [M]⁺ (3 × ³⁷Cl)), 278 (2, [M-H]⁺ (3 × ³⁷Cl)), 277 (21, [M]⁺ (1 × ³⁵Cl + 2 × ³⁷Cl)), 276 (6, [M-H]⁺ (1 × ³⁵Cl + 2 × ³⁷Cl)), 275 (55, [M]⁺ (2 × ³⁵Cl + 1 × ³⁷Cl)), 274 (5, [M-H]⁺ (2 × ³⁵Cl + 1 × ³⁷Cl)), 273 (56, [M]⁺ (3 × ³⁵Cl)) 177 (48, [C₁₀H₆NCl]⁺ (1 × ³⁷Cl)), 175 (100, [C₁₀H₆NCl]⁺ (1 × ³⁵Cl)), 142 (41, [C₉H₆N]⁺), 89 (20, [C₆H₃N]⁺), 77 (82, [C₆H₅]⁺), 65 (32), 51 (72), 39 (24).

The minor product was identified as *4,5,6-trichloro-N-phenylpyridazin-3-amine 302b* (0.14g, 6%) as a orange solid; mp 135 – 136°C (Found C, 43.6%; H, 2.3; N, 15.7. C₁₀H₆N₃Cl₃ requires C, 43.8; H, 2.2; N, 15.3%); δ_{H} (400MHz, CDCl₃) 6.96 (1H, br s, NH), 7.15 (1H, t, ³J_{HH} 7.8, C4'(H)), 7.39 (2H, t, ³J_{HH} 7.8, C2'(H)), 7.68 (2H, d, ³J_{HH} 7.8, C3'(H)); δ_{C} (100MHz, CDCl₃) 120.9 (s, PhC), 124.6 (s, PhC), 129.4 (s, PhC), 135.2 (s), 138.1 (s, PhC), 146.4 (s), 153.2 (s), 154.9 (s); *m/z* (EI⁺) 279 (1%, [M]⁺ (3 × ³⁷Cl)), 278 (5, [M-H]⁺ (3 × ³⁷Cl)), 277 (9, [M]⁺ (1 × ³⁵Cl + 1 × ³⁷Cl)), 276 (34, [M-H]⁺ (1 × ³⁵Cl + 1 × ³⁷Cl)), 275

(20, $[M]^+$ ($2 \times {}^{35}\text{Cl} + 1 \times {}^{37}\text{Cl}$)), 274 (100, $[M-H]^+$ ($2 \times {}^{35}\text{Cl} + 1 \times {}^{37}\text{Cl}$)), 273 (20, $[M]^+$ ($3 \times {}^{35}\text{Cl}$)), 272 (98, $[M-H]^+$ ($3 \times {}^{35}\text{Cl}$)), 177 (8, $[\text{C}_{10}\text{H}_6\text{NCl}]^+$ ($1 \times {}^{37}\text{Cl}$)), 175 (24, $[\text{C}_{10}\text{H}_6\text{NCl}]^+$ (${}^{35}\text{Cl}$)), 77 (59, $[\text{C}_6\text{H}_5]^+$), 65 (25, $[\text{C}_5\text{H}_5]^+$), 51 (58), 39 (18). Crystals suitable for X-ray diffraction were grown by slow evaporation of dichloromethane.

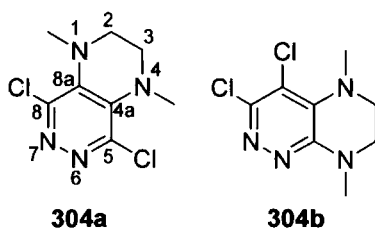
4,6-Dichloro-N3,N3,N5,N5-tetraethylpyridazine-3,5-diamine 303



303

3,5,6-trichloro-N,N-diethylpyridazin-4-amine (0.50g, 1.96mmol) was dissolved in acetonitrile (5ml) under argon with stirring. Diethylamine (0.41ml, 3.92mmol) was added and the mixture irradiated in a sealed microwave vial at 150°C for 30 minutes. Water (20ml) was added and the solution acidified with 10% HCl, followed by extraction with ethyl acetate ($3 \times 20\text{ml}$). The combined organic extracts were dried (MgSO_4), filtered and evaporated under vacuum to yield a crude red-brown product. This was then purified by flash column chromatography using ethyl acetate and hexane (1:2) as elutant to yield 4,6-dichloro-N3,N3,N5,N5-tetraethylpyridazine-3,5-diamine **303** (0.35g, 62%) as a yellow oil; (Found C, 49.8; H, 6.8; N, 19.4. $\text{C}_{12}\text{H}_{20}\text{N}_4\text{Cl}_2$ requires C, 49.5; H, 6.9; N, 19.2%); δ_{H} (CDCl_3 , 400MHz) 0.98 (3H, t, ${}^3J_{\text{HH}}$ 6.8, CH_3), 1.13 (3H, t, ${}^3J_{\text{HH}}$ 6.5, CH_3), 3.23 (2H, q, ${}^3J_{\text{HH}}$ 6.8, CH_2), 3.38 (2H, q, ${}^3J_{\text{HH}}$ 6.5, CH_2); δ_{C} (CDCl_3 , 125MHz) 12.9 (s, CH_2), 13.9 (s, CH_2), 44.7 (s, CH_3), 45.9 (s, CH_3), 126.9 (s, ArC), 145.5 (s, ArC), 149.2 (s, ArC), 161.0 (s, ArC); m/z (EI) 294 (1%, M^+ ($2 \times {}^{37}\text{Cl}$)), 292 (6, M^+ ($1 \times {}^{37}\text{Cl}$, $1 \times {}^{35}\text{Cl}$)), 290 (10, M^+ ($2 \times {}^{35}\text{Cl}$)), 72 (70, $[\text{NEt}_2]^+$), 29 (100, $[\text{CH}_2\text{CH}_3]^+$).

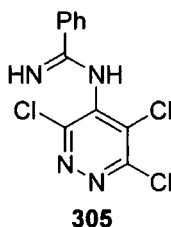
*5,8-Dichloro-1,2,3,4-tetrahydro-1,4-dimethylpyrazino[2,3-*d*]pyridazine* **304a** and *3,4-dichloro-5,6,7,8-tetrahydro-5,8-dimethylpyrazino[2,3-*c*]pyridazine* **304b**



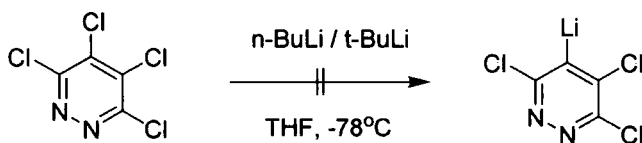
Tetrachloropyridazine (1.00g, 4.59mmol) was dissolved in acetonitrile (100ml) under argon with stirring. N,N'-dimethylethylenediamine (0.54ml, 5.05mmol) was added and the mixture stirred at room temperature for 65 hours. At the end of this period, water (25ml) was added and the solution acidified with 10% HCl, followed by extraction with ethyl acetate (4 × 25ml). The combined organic extracts were dried (MgSO₄), filtered and evaporated under vacuum to yield a crude red-brown product (0.98g). This was then purified by flash column chromatography (Elutant = Hexane : Ethyl Acetate (1:1 – 1200ml) followed by Hexane : Ethyl Acetate (1:2 – 600ml). This yielded 2 products in an isomer ratio of 2.66 : 1 from the crude ¹H NMR.

The major product was *5,8-dichloro-1,2,3,4-tetrahydro-1,4-dimethylpyrazino[2,3-*d*]pyridazine* **304a** (0.34g, 32%) as a cream solid; mp 143.5 – 146°C (Found C, 41.2; H, 4.3; N, 23.8. C₈H₁₀N₄Cl₂ requires C, 41.2; H, 4.3; N, 24.0%); ν_{\max} / cm⁻¹ 984, 1037, 1074, 1115, 1213, 1240, 1307, 1331, 1362, 1420, 1450, 1491, 2878 (CH); δ_{H} (CDCl₃, 500MHz) 3.05 (3H, s, CH₃), 3.07 (2H, s, CH₂CH₂); δ_{C} (CDCl₃, 100MHz) 42.7 (s, CH₂CH₂), 46.1 (s, CH₃), 135.7 (s, C4a/8a), 146.0 (s, C5/8); *m/z* (EI) 233 (0.4%, [M]⁺ (1 × ³⁷Cl, 1 × ³⁵Cl)), 231 (1.6, [M]⁺ (2 × ³⁵Cl)), 91 (100). Crystals suitable for X-ray diffraction were obtained from slow evaporation of ethyl acetate.

The minor product was *3,4-dichloro-5,6,7,8-tetrahydro-5,8-dimethylpyrazino[2,3-*c*]pyridazine* **304a** (0.18g, 17%) as a cream solid; mp 121 – 123°C (Found C, 42.5; H, 4.7; N, 22.7; C₈H₁₀N₄Cl₂ requires C, 41.2; H, 4.3; N, 24.0%); δ_{H} (CDCl₃, 400MHz) 3.40 (2H, m, CH₂), 3.35 (2H, m, CH₂), 3.20 (3H, s, CH₃), 3.16 (3H, s, CH₃); δ_{C} (CDCl₃, 100MHz) 36.9 (s, CH₂), 41.8 (s, CH₂), 45.4 (s, CH₃), 50.1 (s, CH₃), 134.4 (s), 136.9 (s), 145.5 (s), 150.5 (s), 153.9 (s); *m/z* (EI⁺) 217 ([M-Me]⁺, 1%), 106 (28), 85 ([C₅H₉N₂⁺], 29), 71 ([C₃H₇N₂⁺], 34), 49 (32), 47 (100), 35 (72).

N-(3,5,6-Trichloropyridazin-4-yl)benzamidinium **305**

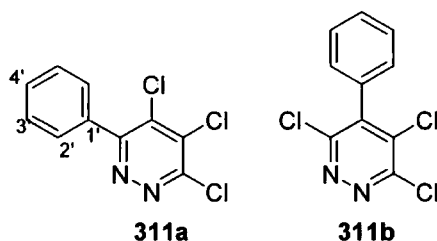
Tetrachloropyridazine (1.00g, 4.59mmol) was dissolved in acetonitrile (100ml) under argon with stirring. Benzamidinium hydrochloride (0.79g, 5.05mmol) and sodium hydrogen carbonate (1.54g, 18.36mmol) were added and formed a suspension, which was heated to 80°C for 22 hours. After this period a yellow solution was obtained, from which the solvent was evaporated and the residue dissolved in ethyl acetate (50ml). This was washed with water (25ml), and the aqueous layer extracted with ethyl acetate (3 × 25ml). The combined organic extracts were dried (MgSO₄), filtered and evaporated *in vacuo* to yield a crude brown material. This was recrystallised from ethyl acetate and hexane (1:1) to give *N*-(3,5,6-trichloropyridazin-4-yl)benzamidinium **305** (0.58g, 43%); as yellow solid, mp 179 – 181°C (Found C, 43.5; H, 2.6; N, 18.8; C₁₁H₇N₄Cl₃ requires C, 43.8; H, 2.3; N, 18.6%). δ_{H} (400MHz, DMSO-*d*₆) 7.16 (1H, br s, NH), 7.61 – 7.46 (4H, m, ArH + NH), 7.97 (2H, d, ³J_{HH} 7.4, ArH); δ_{C} (100MHz, DMSO-*d*₆) 128.0 (s), 128.8 (s), 131.9 (s), 133.9 (s), 148.6 (s), 151.2 (s), 153.9 (s), 157.1 (s); *m/z* (EI⁺) 304 (6%, M⁺ (2 × ³⁷Cl, 1 × ³⁵Cl)), 302 (17, M⁺ (1 × ³⁷Cl, 2 × ³⁵Cl)), 300 (17, M⁺ (3 × ³⁵Cl)), 269 (4, [M – Cl]⁺, (2 × ³⁷Cl)), 267 (20, [M – Cl]⁺, (1 × ³⁷Cl, 1 × ³⁵Cl)), 265 (32, [M – Cl]⁺, (2 × ³⁵Cl)), 104 (100, [PhCNH]⁺), 77 (80, [Ph]⁺), 51 (37).

Attempted lithiation of tetrachloropyridazine

Tetrachloropyridazine (1g, 4.59mmol) was dissolved in THF (20ml) under argon with stirring, and the mixture cooled to -78°C. *n*-Butyllithium (4.59mmol) was added dropwise, and the solution was observed to darken to a deep brown. After stirring for 2 hours, water (10ml) was added, and the solution allowed to warm to room temperature. The mixture was then extracted with dichloromethane (3 × 20ml), and the combined organic extracts were dried (MgSO₄), filtered and evaporated to yield a tarry, brown

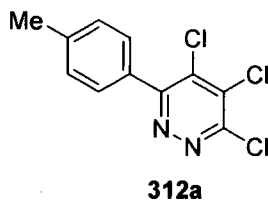
material. GC and ^{13}C NMR analysis showed this to be an extremely complex mixture, so product purification was not attempted.

3,4,5-Trichloro-6-phenylpyridazine 311a and 3,4,6-trichloro-5-phenylpyridazine 311b

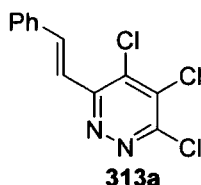


Tetrachloropyridazine (2.00g, 9.18mmol), phenyl boronic acid (1.12g, 9.18mmol), caesium carbonate (5.98g, 18.35mmol) and $\text{Pd}(\text{PPh}_3)_4$ (0.53g, 0.46mmol, 5mol%) were dissolved in dry toluene (50ml) that has been degassed by the freeze-pump-thaw technique. The mixture was then heated to reflux for 16 hours, before being allowed to cool to room temperature. Water (50ml) was added, and the mixture extracted with dichloromethane ($3 \times 50\text{ml}$). The combined organic extracts were dried (MgSO_4), filtered and evaporated *in vacuo* to yield a crude brown material (2.34g). This was then purified by flash column chromatography (Hexane : DCM, 2:1) to yield the major product *3,4,5-trichloro-6-phenylpyridazine 311a* (0.76g, 32%) as white crystals; mp $98 - 101^\circ\text{C}$ (Found C, 46.4; H, 2.2; N, 10.5. $\text{C}_{11}\text{H}_8\text{N}_3\text{Cl}_3$ requires C, 46.3; H, 1.9; N, 10.8%); $\nu_{\text{max}} / \text{cm}^{-1}$ 1059, 1077, 1169, 1225, 1268, 1277, 1442, 1474, 1487; δ_{H} (CDCl_3 , 500MHz) 7.29 (2H, dd, $^3J_{\text{HH}}$ 7.0, $^3J_{\text{HH}}$ 4.1, C3'(H), 7.55 (3H, m, C2'+4'(H)); δ_{C} (CDCl_3 , 125MHz) 116.0 (s), 128.5 (s, PhC), 129.1 (s, PhC), 130.3 (s, PhC), 132.1 (s, PhC), 138.1 (s), 141.4 (s), 155.6 (s); m/z (EI^+) 264 (1%, M^+ ($3 \times ^{37}\text{Cl}$)), 262 (18, M^+ ($2 \times ^{37}\text{Cl}$, $1 \times ^{35}\text{Cl}$)), 260 (48, M^+ ($1 \times ^{37}\text{Cl}$, $2 \times ^{35}\text{Cl}$)), 258 (46, M^+ , $3 \times ^{35}\text{Cl}$), 236 (1, $[\text{M}-\text{N}_2]^+$ ($3 \times ^{37}\text{Cl}$)), 234 (15, $[\text{M}-\text{N}_2]^+$ ($2 \times ^{37}\text{Cl}$, $1 \times ^{35}\text{Cl}$)), 232 (40, $[\text{M}-\text{N}_2]^+$ ($1 \times ^{37}\text{Cl}$, $2 \times ^{35}\text{Cl}$)), 230 (38, $[\text{M}-\text{N}_2]^+$, $3 \times ^{35}\text{Cl}$), 197 (42), 195 (58), 160 (100).

The minor isomer was *3,4,6-trichloro-5-phenylpyridazine 311b* (0.21g, 9%) as white solid; mp $119 - 121^\circ\text{C}$ (Found C, 46.5; H, 2.2; N, 10.4. $\text{C}_{11}\text{H}_8\text{N}_3\text{Cl}_3$ requires C, 46.3; H, 1.9; N, 10.8%); $\nu_{\text{max}} / \text{cm}^{-1}$ 1020, 1072, 1262, 3567; δ_{H} (CDCl_3 , 400MHz) 7.53 (3H, m, C3'+4'(H)), 7.72 (2H, m, C2'(H)); δ_{C} (CDCl_3 , 100MHz) 128.4 (s), 128.5 (s, PhC), 129.5 (s, PhC), 130.3 (s, PhC), 134.0 (s, PhC), 136.8 (s), 157.9 (s), 159.8 (s); m/z (EI^+) 264 (2%, $[\text{M}]^+$ ($3 \times ^{37}\text{Cl}$)), 262 (20, $[\text{M}]^+$ ($2 \times ^{37}\text{Cl}$, $1 \times ^{35}\text{Cl}$)), 260 (53, $[\text{M}]^+$ ($1 \times ^{37}\text{Cl}$, $2 \times ^{35}\text{Cl}$)), 258 (50, $[\text{M}]^+$, ($3 \times ^{35}\text{Cl}$)), 197 (33), 195 (40), 160 (100).

3,4,5-Trichloro-6-*p*-tolylpyridazine 312a

Tetrachloropyridazine (1.00g, 4.59mmol), *p*-tolyl boronic acid (0.62g, 4.59mmol), caesium carbonate (2.99g, 9.18mmol) and Pd(PPh₃)₄ (0.27g, 0.23mmol, 5mol%) were dissolved in dry toluene (50ml) that has been degassed by the freeze-pump-thaw technique. The mixture was then heated to reflux for 16 hours, before being allowed to cool to room temperature. Water (20ml) was added, and the mixture extracted with dichloromethane (3 × 20ml). The combined organic extracts were dried (MgSO₄), filtered and evaporated *in vacuo* to yield a crude brown material. Purification was attempted by flash column chromatography (Hexane : DCM, 2:1), however the major product was not isolated pure. It is likely the major product was 3,4,5-trichloro-6-*p*-tolylpyridazine **312a** (0.30g, 24%); δ_{H} (400MHz, CDCl₃) 2.31 (3H, s, CH₃), 7.18 (4H, m, ArH); m/z (EI) 278 (6%, [M]⁺ (3 × ³⁷Cl)), 276 (53, [M]⁺ (2 × ³⁷Cl, 1 × ³⁵Cl)), 274 (70, [M]⁺ (1 × ³⁷Cl, 2 × ³⁵Cl)), 272 (61, [M]⁺, 3 × ³⁵Cl), 173 (100), 139 (80), 86 (58).

3,4,5-Trichloro-6-styrylpyridazine 313a

Tetrachloropyridazine (1.00g, 4.59mmol), (*Z*)-phenyl-vinyl boronic acid (0.68g, 4.59mmol), caesium carbonate (2.99g, 9.18mmol) and Pd(PPh₃)₄ (0.27g, 0.23mmol, 5mol%) were dissolved in dry toluene (50ml) that has been degassed by the freeze-pump-thaw technique. The mixture was then heated to reflux for 16 hours, before being allowed to cool to room temperature. Water (20ml) was added, and the mixture extracted with dichloromethane (3 × 20ml). The combined organic extracts were dried (MgSO₄), filtered and evaporated *in vacuo* to yield a crude brown material. Purification was attempted by flash column chromatography (Hexane : DCM, 2:1), however the major product was not isolated pure. It is likely the major product was 3,4,5-trichloro-6-styrylpyridazine **313a**.

(0.43g, 33%); δ_{H} (400MHz, CDCl_3) 7.34 (3H, m, ArH), 7.38 (1H, d, $^3J_{\text{HH}}$ 16.6, CH=), 7.58 (2H, d, $^3J_{\text{HH}}$ 8.0, ArH), 8.12 (1H, d, $^3J_{\text{HH}}$ 16.6, CH=); δ_{C} (100MHz, CDCl_3) 118.4 (s), 128.0 (s), 129.0 (s), 129.9 (s), 135.6 (s), 136.0 (s), 137.5 (s), 139.7 (s), 152.7 (s), 155.6 (s); m/z (EI) 290 (4%, $[\text{M}]^+$ ($3 \times {}^{37}\text{Cl}$)), 288 (22, $[\text{M}]^+$ ($2 \times {}^{37}\text{Cl}$, $1 \times {}^{35}\text{Cl}$), 286 (100, $[\text{M}]^+$ ($1 \times {}^{37}\text{Cl}$, $2 \times {}^{35}\text{Cl}$)), 284 (80, $[\text{M}]^+$, ($3 \times {}^{35}\text{Cl}$)), 258 (33), 150 (41).

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